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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under **37 CFR 1.53** (c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Wei	Han	West Chester, PA
Melissa	Egbertson	Ambler, PA
John S.	Wai	Harleysville, PA
Linghang	Zhuang	Chalfont, PA
Rowena D.	Ruzek	North Wales, PA
Debra S.	Perlow	East Greenville, PA
Richard C. A.	Isaacs	Harleysville, PA

☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

HIV INTEGRASE INHIBITORS

CORRESPONDENCE ADDRESS

Direct all Correspondence to:

Merck & Co., Inc.
Patent Department - RY60-30
P.O. Box 2000
Rahway

☒ Customer Number 000210

STATE	New Jersey	ZIP CODE	07065	COUNTRY	U.S.A.

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Respectfully submitted,

SIGNATURE Kenneth R. Walton

Date 12/03/2004

TYPED or PRINTED NAME Kenneth R. Walton

REGISTRATION NO. *(if appropriate)* 32,951

TELEPHONE 732 594-3462

EXPRESS MAIL CERTIFICATE

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PROVISIONAL APPLICATION COVER SHEET

Additional Page

First Named Inventor	Wei Han	Docket Number	21515PV2

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Mark	Cameron	Brick, NJ
Bruce S.	Foster	Scoth Plains, NJ
Ulf H.	Dolling	Westfield, NJ
R. Scott	Hoerrner	Westfield, NJ

NUMBER _____ of _____

TITLE OF THE INVENTION

HIV INTEGRASE INHIBITORS

The present invention is directed hydroxy tetrahydro-2,6-naphthyridine dione and hydroxy hexahydro-2,6-naphthyridine dione compounds and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds and pharmaceutically acceptable salts thereof of the present invention are useful for preventing or treating infection by HIV and for preventing or treating or delaying the onset of AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) virus and type-2 (HIV-2) virus, is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of +proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

US 6380249, US 6306891, and US 6262055 disclose 2,4-dioxobutyric acids and acid esters useful as HIV integrase inhibitors.

WO 01/00578 discloses 1-(aromatic- or heteroaromatic-substituted)-3-(heteroaromatic substituted)-1,3-propanediones useful as HIV integrase inhibitors.

US 2003/0055071 (corresponding to WO 02/30930), WO 02/30426, and WO 02/55079 each disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors.

WO 02/036734 discloses certain aza- and polyaza-naphthalenyl ketones to be HIV integrase inhibitors.

WO 03/016275 discloses certain compounds having integrase inhibitory activity.

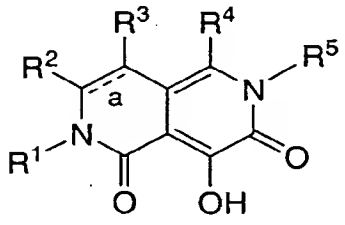
WO 03/35076 discloses certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors, and WO 03/35077 discloses certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

WO 03/062204 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

WO 04/004657 discloses certain hydroxypyrrole derivatives that are HIV integrase inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to hydroxy polyhydro-2,6-naphthyridine dione compounds. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof:



(I)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl optionally substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$OC(=O)N(R^a)R^b$, or -$N(R^a)C(=O)N(R^a)R^b$,

(2) -O-C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halogen,

(7) -CN,

(8) -NO_2,

(9) -$N(R^a)R^b$,

(10) -$C(=O)N(R^a)R^b$,

(11) -$C(=O)R^a$,

(12) -CO_2R^a,

(13) -SR^a,

(14) -$S(=O)R^a$,

(15) -SO_2R^a,

(16) -$SO_2N(R^a)R^b$,

(17) -$N(R^a)SO_2R^b$,

(18) -$N(R^a)SO_2N(R^a)R^b$,

(19) -$N(R^a)C(=O)R^b$,

(20) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$, or

(21) -$N(R^a)CO_2R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:

(1) phenyl,

(2) benzyl,

(3) -HetA,

(4) -C(=O)-HetA, or

(5) -HetB;

wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is independently oxo or C_{1-6} alkyl; and

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl substituted with aryl;

R^2 and R^3 are each independently -H or -C_{1-6} alkyl;

R^4 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$C(=O)$-$N(R^a)$-C_{1-6} alkylene-OR^b with the proviso that the -$N(R^a)$- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)$-R^b, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$N(R^a)C(=O)N(R^a)R^b$, or -$OC(=O)N(R^a)R^b$,

(5) -$C(=O)R^a$,

(6) -CO_2R^a,

(7) -$C(=O)N(R^a)R^b$,

(8) -C(=O)-N(R^a)-C_{1-6} alkylene-OR^b with the proviso that the -N(R^a)- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety,

(9) -N(R^a)-C(=O)-R^b,

(10) -N(R^a)-C(=O)-C(=O)N(R^a)R^b,

(11) -N(R^a)SO_2R^b,

(12) -N(R^a)SO_2N(R^a)R^b,

(13) -N(R^a)SO_2N(R^a)R^b,

(14) -N(R^a)C(=O)N(R^a)R^b,

(15) -OC(=O)N(R^a)R^b,

(16) -R^K,

(17) -C(=O)-R^K,

(18) -C(=O)N(R^a)-R^K,

(19) -C(=O)N(R^a)-C_{1-6} alkylene-R^K,

(20) -C_{1-6} alkyl substituted with -R^K,

(21) -C_{1-6} alkyl substituted with -C(=O)-R^K,

(22) -C_{1-6} alkyl substituted with -C(=O)N(R^a)-R^K, or

(23) -C_{1-6} alkyl substituted with -C(=O)N(R^a)-C_{1-6} alkylene-R^K;

wherein R^K is

(i) C_{3-8} cycloalkyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(ii) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-N(R^a)R^b, -C_{1-6} alkylene-C(=O)N(R^a)R^b, -C_{1-6} alkylene-C(=O)R^a, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO_2R^a, -$S(O)_nR^a$, or -SO_2N(R^a)R^b;

(iii) HetK, which is a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 6 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(b) optionally substituted with aryl or HetC;

wherein HetC is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(iv) HetL, which is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^5 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(5) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)R^a$, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(6) -C_{1-6} alkyl substituted with HetD, wherein HetD is

(i) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is optionally substituted with

from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl;

each R^b is independently H or C_{1-6} alkyl; and

each n is independently an integer equal to zero, 1, or 2.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of Formula I above, and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts are HIV integrase inhibitors (e.g., HIV-1 integrase inhibitors).

A first embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; and all other variables are as originally defined (i.e., as defined in the Summary of the Invention).

A second embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is phenyl, quinolinyl, isoquinolinyl, cinnolinyl, or quinazolinyl, any of which is:

(a) optionally substituted with from 1 to 4 substituents each of which is independently:

(1) -C_{1-4} alkyl,
(2) -O-C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} haloalkyl,
(5) halogen,
(6) -CN,
(7) -$N(R^a)R^b$,
(8) -$C(=O)N(R^a)R^b$,
(9) -$S(=O)R^a$,
(10) -SO_2R^a,
(11) -$N(R^a)SO_2R^b$,
(12) -$N(R^a)SO_2N(R^a)R^b$,
(13) -$N(R^a)C(=O)R^b$, or
(14) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:
(1) -HetA, or
(2) -C(=O)-HetA;
wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-4} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom;

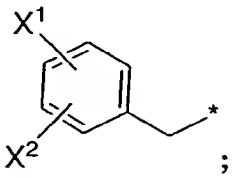
and all other variables are as originally defined.

A third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is phenyl optionally substituted with from 1 to 3 substitutents each of which is independently:

(1) -C_{1-4} alkyl,
(2) -C_{1-4} haloalkyl,
(3) -O-C_{1-4} alkyl,
(4) halogen,
(5) -CN,
(6) -$C(=O)N(R^a)R^b$, or
(7) -SO_2R^a;

and all other variables are as originally defined.

A fourth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



the asterisk * denotes the point of attachment of R^1 to the rest of the compound; X^1 and X^2 are each independently:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -O-C_{1-6} alkyl,
(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} haloalkyl,
(6) halogen,
(7) -CN,
(8) -$N(R^a)R^b$,
(9) -$C(=O)N(R^a)R^b$,
(10) -$S(O)_nR^a$, wherein n is an integer equal to zero, 1, or 2,
(11) -$N(R^a)SO_2R^b$,
(12) -$N(R^a)SO_2N(R^a)R^b$,
(13) -$N(R^a)C(=O)R^b$,
(14) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$,
(15) -HetA,
(16) -C(=O)-HetA, or
(17) HetB;

wherein each HetA is independently a C_{4-5} azacycloalkyl or a C_{3-4} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-6} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom; and

each HetB is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which

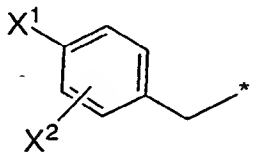
is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

and all other variables are as originally defined.

An aspect of the fourth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 in the definition of R^1 are each independently: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{1-4} haloalkyl, (4) -O-C_{1-4} alkyl, (5) halogen, (6) -CN, (7) -C(=O)NH_2, (8) -C(=O)NH(-C_{1-4} alkyl), (9) -C(=O)N(-C_{1-4} alkyl)$_2$, or (10) -SO_2-C_{1-4} alkyl; and all other variables are as defined in the fourth embodiment.

Another aspect of the fourth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X^1 in the definition of R^1 is (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy; and X^2 in the definition of R^1 is (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methyl, (6) methoxy, (7) -CF_3, or (8) -OCF_3.

A fifth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



the asterisk * denotes the point of attachment of R^1 to the rest of the compound; X^1 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy; X^2 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methoxy, (6) -C_{1-4} alkyl, (7) -CF_3, (8) -OCF_3, (9) -CN, or (10) -SO_2(C_{1-4} alkyl); and all other variables are as originally defined.

An aspect of the fifth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X^1 in the definition of R^1 is (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy; and X^2 in the definition of R^1 is (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methyl, (6) methoxy, (7) -CF_3, or (8) -OCF_3.

A sixth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is 4-fluorophenyl or 3-chloro-4-fluorophenyl; and all other variables are as originally defined.

A seventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is 4-fluorophenyl; and all other variables are as originally defined.

An eighth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is 3-chloro-4-fluorophenyl; and all other variables are as originally defined.

A ninth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{1-6} haloalkyl,
(4) -C_{1-6} alkyl substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)$-R^b, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$N(R^a)C(=O)N(R^a)R^b$, or -$OC(=O)N(R^a)R^b$,
(5) -$C(=O)R^a$,
(6) -CO_2R^a,
(7) -$C(=O)N(R^a)R^b$,
(8) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b,
(9) -$N(R^a)$-$C(=O)$-R^b,
(10) -$N(R^a)$-$C(=O)$-$C(=O)N(R^a)R^b$,
(11) -$N(R^a)SO_2R^b$,
(12) -$N(R^a)SO_2N(R^a)R^b$,
(13) -R^K,
(14) -$C(=O)$-R^K,
(15) -$C(=O)N(R^a)$-R^K,
(16) -$C(=O)N(R^a)$-C_{1-6} alkylene-R^K,
(17) -$(CH_2)_{1-3}$-R^K,
(18) -$(CH_2)_{1-3}$-$C(=O)$-R^K,
(19) -$(CH_2)_{1-3}$-$C(=O)N(R^a)$-R^K, or
(20) -$(CH_2)_{1-3}$-$C(=O)N(R^a)$-C_{1-6} alkylene-R^K;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A tenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -H, (2) -C_{1-6} alkyl, (3) -C_{1-6} fluoroalkyl, (4) -CO_2R^a, (5) -$C(=O)N(R^a)R^b$, (6) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b, (7) -$N(R^a)$-$C(=O)$-R^b, (8) -$N(R^a)SO_2R^b$, (9) -$N(R^a)SO_2N(R^a)R^b$, (10) -R^K, (11) -$C(=O)$-R^K, or (12) -$C(=O)N(R^a)$-$(CH_2)_{0-2}$-R^K; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An aspect of either the ninth or the tenth embodiment is a compound of Formula I, or a pharmaceutically acceptable thereof, wherein R^K is:

(i) C_{3-6} cycloalkyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(ii) phenyl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)R^a$, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(iii) HetK, which is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(iv) HetL, which is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl;

and all other variables are as defined in the ninth or the tenth embodiment.

An eleventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -H, (2) -C_{1-4} alkyl, (3) -CO_2H, (4) -C(=O)-O-C_{1-4} alkyl, (5) -$C(=O)NH_2$, (6) -C(=O)NH-C_{1-4} alkyl, (7) -$C(=O)N(C_{1-4}$ alkyl$)_2$, (8) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (9) -C(=O)-$N(C_{1-4}$ alkyl$)$-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (10) -HetK, (11) -C(=O)-HetK, (12) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (13) -C(=O)$N(C_{1-4}$ alkyl$)$-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl) (14) -C(=O)NH-CH_2-phenyl, or (15) -C(=O)$N(C_{1-4}$ alkyl$)$-CH_2-phenyl; wherein:

HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

the cycloalkyl in (12) or (13) is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -CF_3, -O-C_{1-4} alkyl, or -OCF_3; and

the phenyl in (14) or (15) is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -O-C_{1-4} alkyl, -CF_3, or -OCF_3;

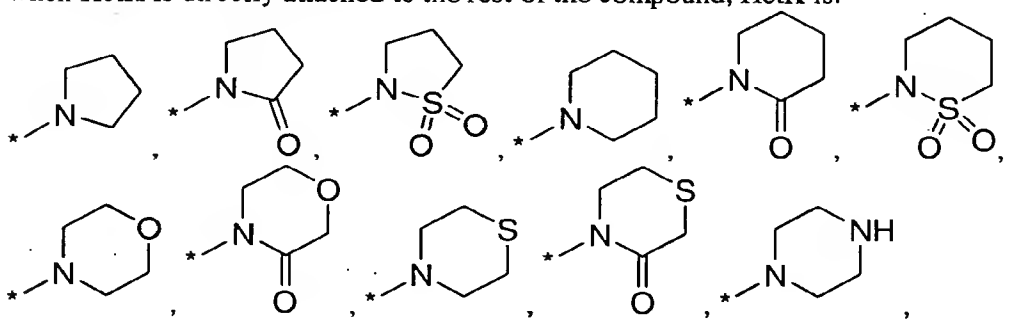
and all other variables are as originally defined or as defined in any one of the preceding embodiments.

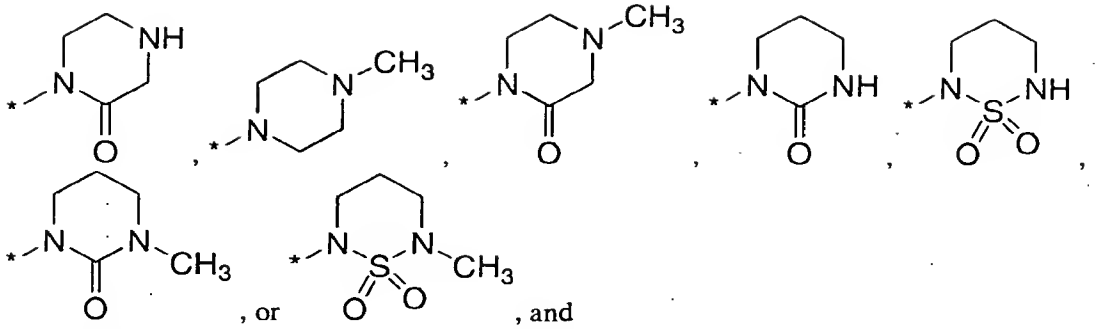
A twelfth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -CO_2R^a, (2) -C(=O)N(R^a)R^b, (3) -C(=O)-N(R^a)-$(CH_2)_{2-3}$-OR^b, (4) -N(R^a)C(=O)R^b, (5) -N(R^a)SO_2R^b, (6) -HetK, (7) -C(=O)-HetK, (8) -C(=O)N(R^a)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -CF_3, -O-C_{1-6} alkyl, or -OCF_3, or (9) -C(=O)N(R^a)-CH_2-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -O-C_{1-6} alkyl, -CF_3, -OCF_3, or halogen; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An aspect of the twelfth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom; and all other variables are as defined in the twelfth embodiment.

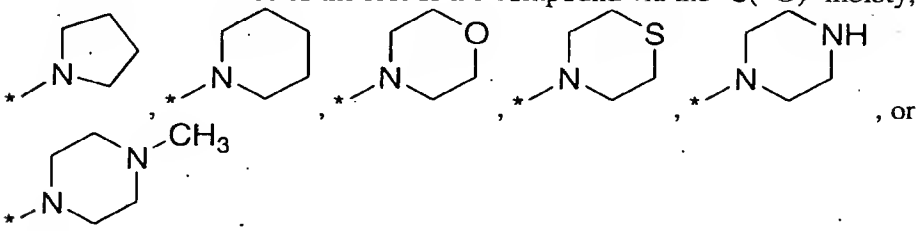
Another aspect of the twelfth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

(a) when HetK is directly attached to the rest of the compound, HetK is:



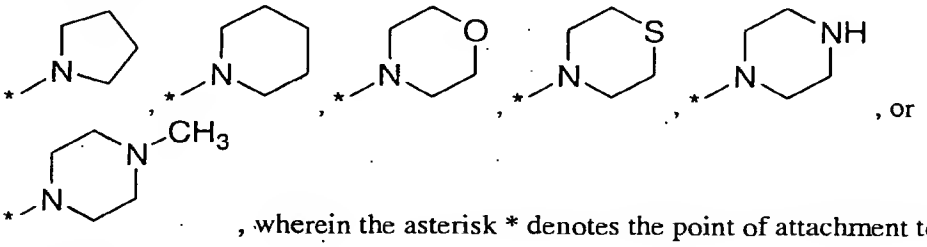


(b) when HetK is attached to the rest of the compound via the -C(=O)- moiety, HetK is:



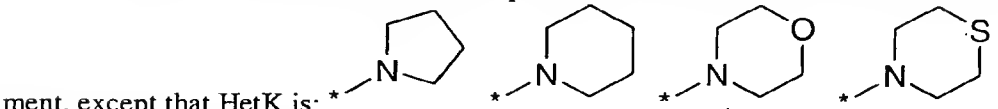
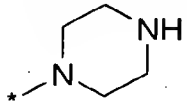
wherein the asterisk * denotes the point of attachment to the rest of the compound; and all other variables are as defined in the twelfth embodiment.

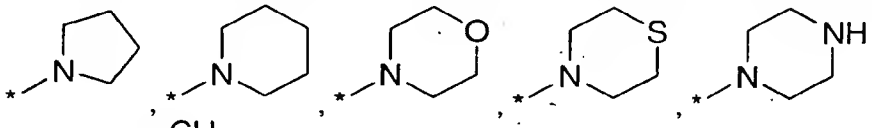
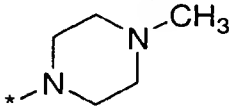
A thirteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) $-CO_2H$, (2) $-C(=O)-O-C_{1-4}$ alkyl, (3) $-C(=O)NH_2$, (4) $-C(=O)NH-C_{1-4}$ alkyl, (5) $-C(=O)N(C_{1-4}$ alkyl$)_2$, (6) $-C(=O)-NH-(CH_2)_{2-3}-O-C_{1-4}$ alkyl, (7) $-C(=O)-N(C_{1-4}$ alkyl$)-(CH_2)_{2-3}-O-C_{1-4}$ alkyl, (8) $-NHC(=O)-C_{1-4}$ alkyl, (9) $-N(C_{1-4}$ alkyl$)C(=O)-C_{1-4}$ alkyl, (10) $-NHSO_2-C_{1-4}$ alkyl, (11) $-N(C_{1-4}$ alkyl$)SO_2-C_{1-4}$ alkyl, (12) -C(=O)-HetK, wherein HetK is:



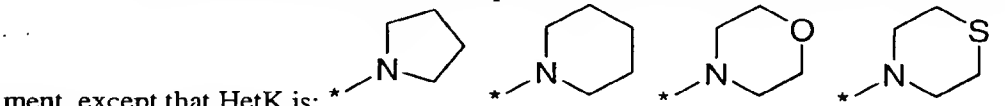
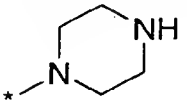
, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) $-C(=O)NH-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), (14) $-C(=O)N(C_{1-4}$ alkyl$)-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), (15) $-C(=O)NH-CH_2$-phenyl, or (16) $-C(=O)N(C_{1-4}$ alkyl$)-CH_2$-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A fourteenth embodiment of the present invention is identical to the thirteenth embodiment, except that HetK is:  , or 

A fifteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -C(=O)-O-C_{1-3} alkyl, (2) -C(=O)NH-C_{1-3} alkyl, (3) -C(=O)N(C_{1-3} alkyl)$_2$, (4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl, (5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl, (6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl, (7) -C(=O)-HetK, wherein HetK is:  , or  , wherein the asterisk * denotes the point of attachment to the rest of the compound,

(8) -C(=O)NH-(CH2)0-1-(cyclopropyl), (9) -C(=O)NH-(CH2)0-1-(cyclobutyl), (10) -C(=O)N(C1-3 alkyl)-$(CH_2)_{0-1}$-cyclopropyl, (11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl, (12) -C(=O)NH-CH_2-phenyl, or (13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A sixteenth embodiment of the present invention is identical to the fifteenth embodiment, except that HetK is:  , or 

A seventeenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,

(2) -C_{1-4} alkyl,

(3) -C_{3-6} cycloalkyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

(4) -$(CH_2)_{1-2}$-C_{3-6} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

(5) -$(CH_2)_{1-2}$-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} alkylene-O-C_{1-4} alkyl, -C_{1-4} haloalkyl, or -O-C_{1-4} haloalkyl, or

(6) -$(CH_2)_{1-2}$-HetD;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An aspect of the seventeenth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein: HetD is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or hydroxy; and all other variables are as defined in the seventeenth embodiment. In a feature of this aspect, all other variables are as defined in the twelfth embodiment (or an aspect thereof).

An eighteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{3-6} cycloalkyl, (4) -CH_2-C_{3-6} cycloalkyl, or (5) -CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A nineteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) cyclopropyl, (4) cyclobutyl, (5) -CH_2-cyclopropyl, (6) -CH_2-cyclobutyl, or (5) -CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twentieth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is -H or -C_{1-4} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In an aspect of this embodiment, R^5 is -C_{1-4} alkyl. In other aspect of this embodiment, R^5 is methyl, isopropyl, or isobutyl.

A twenty-first embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is -H; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

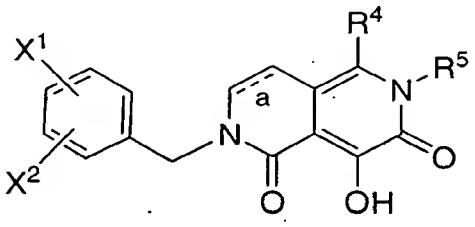
A twenty-second embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both -H; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twenty-third embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently H or C_{1-3} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twenty-fourth embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently H or methyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twenty-fifth embodiment of the present invention is a compound of Formula I, wherein bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A first class of the present invention includes compounds of Formula II, and pharmaceutically acceptable salts thereof:



(II)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

X^1 and X^2 are each independently:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -O-C_{1-6} alkyl,
(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} haloalkyl,
(6) halogen,
(7) -CN,
(8) -$N(R^a)R^b$,
(9) -$C(=O)N(R^a)R^b$,
(10) -$S(O)_nR^a$, wherein n is an integer equal to zero, 1, or 2,
(11) -$N(R^a)SO_2R^b$,
(12) -$N(R^a)SO_2N(R^a)R^b$,

(13) -N(R^a)C(=O)R^b,

(14) -N(R^a)C(=O)-C(=O)N(R^a)R^b,

(15) -HetA,

(16) -C(=O)-HetA, or

(17) HetB;

wherein each HetA is independently a C_{4-5} azacycloalkyl or a C_{3-4} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-6} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom; and

each HetB is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^4 is:

(1) -CO_2R^a,

(2) -C(=O)N(R^a)R^b,

(3) -C(=O)-N(R^a)-$(CH_2)_{2-3}$-OR^b,

(4) -N(R^a)C(=O)R^b,

(5) -N(R^a)SO_2R^b,

(6) -HetK,

(7) -C(=O)-HetK,

(8) -C(=O)N(R^a)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -CF_3, -O-C_{1-6} alkyl, or -OCF_3, or

(9) -C(=O)N(R^a)-CH_2-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -O-C_{1-6} alkyl, -CF_3, -OCF_3, or halogen;

wherein HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is

independently -C_{1-6} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

R^5 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{3-6} cycloalkyl,
(4) -CH_2-C_{3-6} cycloalkyl, or
(5) -CH_2-phenyl;

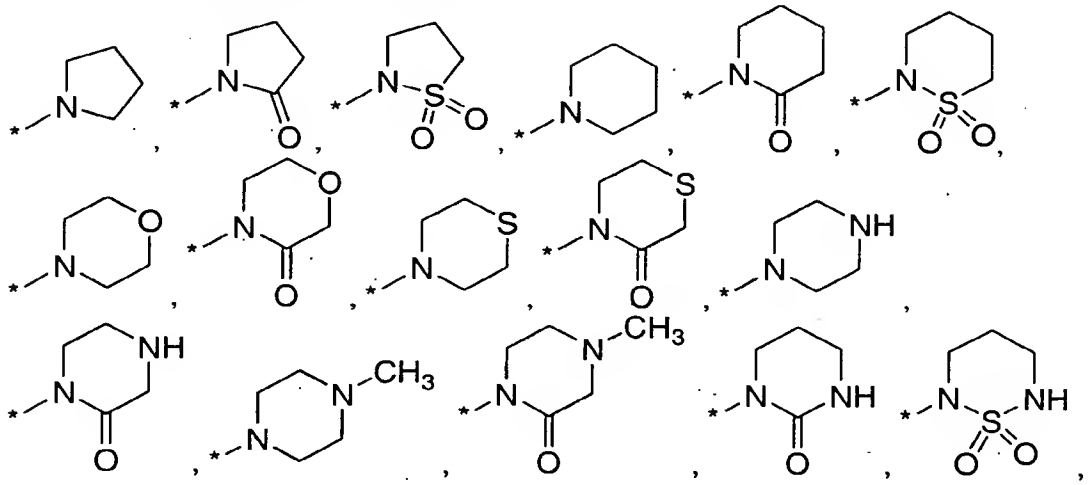
each R^a is independently H or C_{1-6} alkyl; and

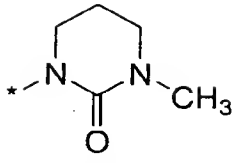
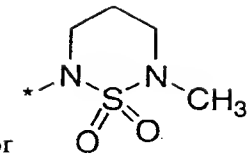
each R^b is independently H or C_{1-6} alkyl.

A sub-class of the first class includes compounds of Formula II, and pharmaceutically acceptable salts thereof, wherein

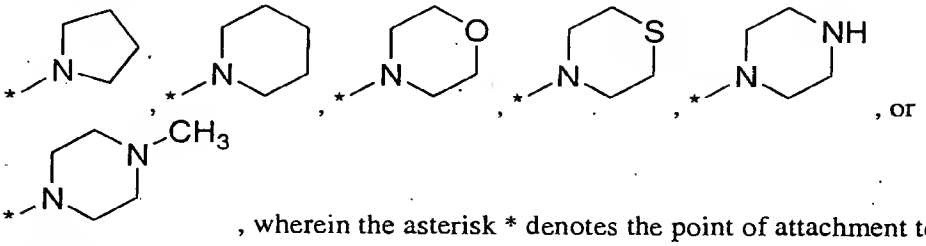
X^1 and X^2 are each independently: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{1-4} haloalkyl, (4) -O-C_{1-4} alkyl, (5) halogen, (6) -CN, (7) -C(=O)NH_2, (8) -C(=O)NH(-C_{1-4} alkyl), (9) -C(=O)N(-C_{1-4} alkyl)$_2$, or (10) -SO_2-C_{1-4} alkyl;

R^4 is: (1) -CO_2H, (2) -C(=O)-O-C_{1-4} alkyl, (3) -C(=O)NH_2, (4) -C(=O)NH-C_{1-4} alkyl, (5) -C(=O)N(C_{1-4} alkyl)$_2$, (6) -C(=O)-NH-(CH_2)$_{2-3}$-O-C_{1-4} alkyl, (7) -C(=O)-N(C_{1-4} alkyl)-(CH_2)$_{2-3}$-O-C_{1-4} alkyl, (8) -NHC(=O)-C_{1-4} alkyl, (9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl, (10) -$NHSO_2$-C_{1-4} alkyl, (11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl, (12) -HetK wherein HetK is:




, or 
, wherein the asterisk * denotes the point of attachment to the rest of the compound,

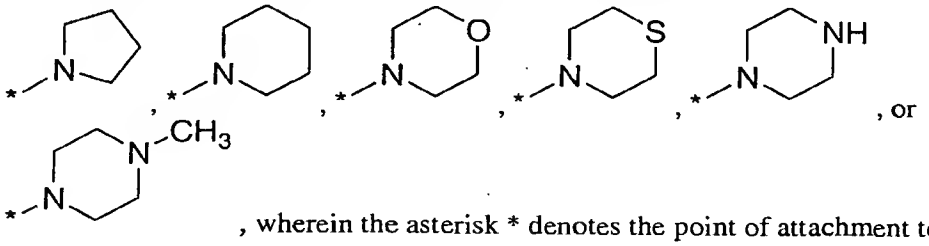
(13) -C(=O)-HetK, wherein HetK is:


, or
, wherein the asterisk * denotes the point of attachment to the rest of the compound,

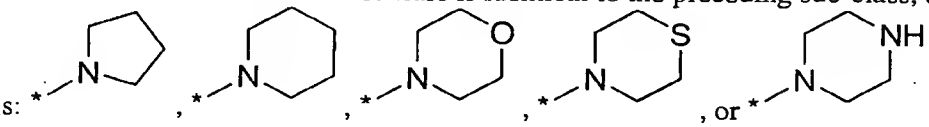
(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (15) -C(=O)NH-CH_2-phenyl, or (16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{3-6} cycloalkyl, (4) -CH_2-C_{3-6} cycloalkyl, or (5) -CH_2-phenyl.

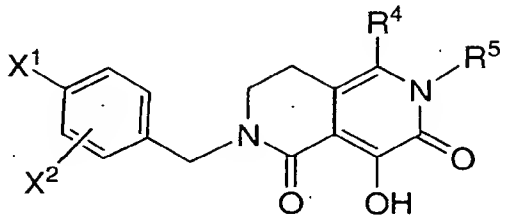
Another sub-class of the first class is identical to the preceding sub-class, except that R^4 is: (1) -CO_2H, (2) -C(=O)-O-C_{1-4} alkyl, (3) -C(=O)NH_2, (4) -C(=O)NH-C_{1-4} alkyl, (5) -C(=O)N(C_{1-4} alkyl)$_2$, (6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (8) -NHC(=O)-C_{1-4} alkyl, (9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl, (10) -$NHSO_2$-C_{1-4} alkyl, (11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl, (12) -C(=O)-HetK, wherein HetK is:


, or
, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (15) -C(=O)NH-CH_2-phenyl, or (16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl.

Still another sub-class of the first class is identical to the preceding sub-class, except that except that HetK is: 
.

A second class of the present invention includes compounds of Formula III, and pharmaceutically acceptable salts thereof:



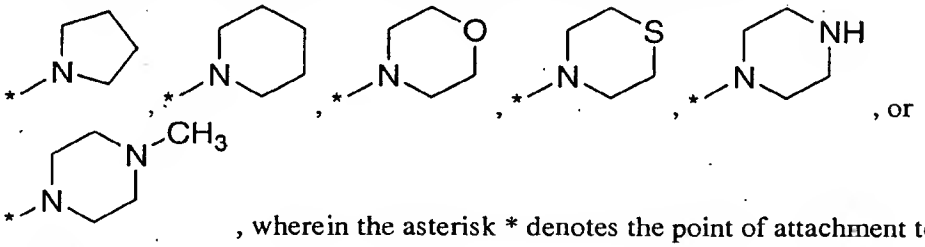
(III)

wherein:

X^1 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy;

X^2 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methoxy, (6) -C_{1-4} alkyl, (7) -CF_3, (8) -OCF_3, (9) -CN, or (10) -$SO_2(C_{1-4}$ alkyl);

R^4 is: (1) -CO_2H, (2) -C(=O)-O-C_{1-4} alkyl, (3) -$C(=O)NH_2$, (4) -C(=O)NH-C_{1-4} alkyl, (5) -$C(=O)N(C_{1-4}$ alkyl$)_2$, (6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (8) -NHC(=O)-C_{1-4} alkyl, (9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl, (10) -$NHSO_2$-C_{1-4} alkyl, (11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl, (12) -C(=O)-HetK, wherein HetK is:

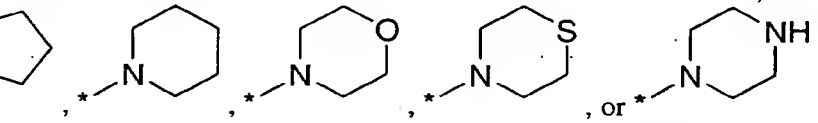


, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (15) -C(=O)NH-CH_2-phenyl, or (16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) cyclopropyl, (4) cyclobutyl, (5) -CH_2-cyclopropyl, (6) -CH_2-cyclobutyl, or (7) -CH_2-phenyl.

A sub-class of the second class is identical to the second class, except that except that HetK is:

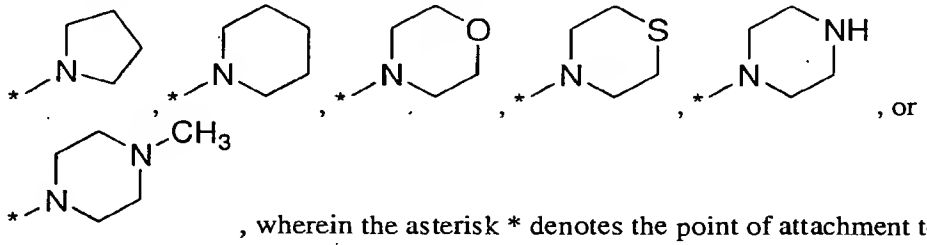


Another sub-class of the second class includes compounds of Formula III, and pharmaceutically acceptable salts thereof, wherein:

X^1 is fluoro;

X^2 is -H or chloro;

R^4 is: (1) -C(=O)-O-C_{1-3} alkyl, (2) -C(=O)NH-C_{1-3} alkyl, (3) -C(=O)N(C_{1-3} alkyl)$_2$, (4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl, (5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl, (6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl, (7) -C(=O)-HetK, wherein HetK is:



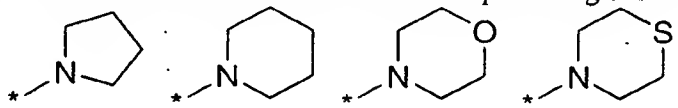
, or

, wherein the asterisk * denotes the point of attachment to the rest of the compound,

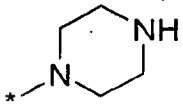
(8) -C(=O)NH-$(CH_2)_{0-1}$-(cyclopropyl), (9) -C(=O)NH-$(CH_2)_{0-1}$-(cyclobutyl), (10) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl, (11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl, (12) -C(=O)NH-CH_2-phenyl, or (13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and

R^5 is -H or C_{1-4} alkyl.

Still another sub-class of the second class is identical to the preceding sub-class, except that X^2 is -H; R^5 is -H; and HetK is:



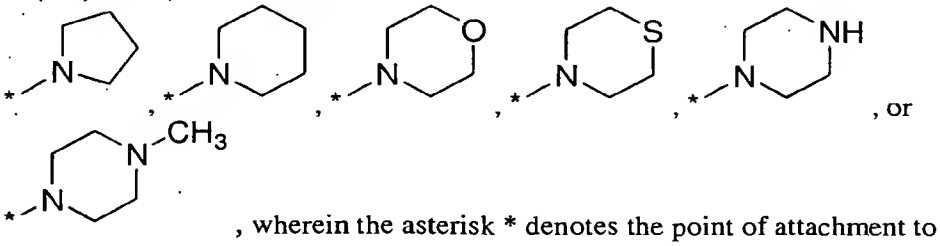
, or



A third class of the present invention includes compounds of Formula III, and pharmaceutically acceptable salts thereof, wherein X^1 is fluoro; X^2 is -H or chloro; R^4 is:

(1) -C(=O)N(C_{1-3} alkyl)$_2$,

(2) -C(=O)-HetK, wherein HetK is:



, or

, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(3) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl, or

(4) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl; and

R^5 is -C_{1-4} alkyl.

Another embodiment of the present invention is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of the compounds set forth in Examples 1 to 16 below. An aspect of this embodiment is a compound, or a pharmaceutically acceptable salt thereof, which is the compound set forth in Example 11, 13, or 14.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A pharmaceutical combination which is (i) a compound of Formula I and (ii) an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of Formula I and the HIV infection/AIDS treatment agent are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(i) The method of (h), wherein the compound of Formula (I) is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(k) The method of (j), wherein the compound is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "alkylene" refers to any linear or branched chain alkylene group (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example,

"-C_{1-6} alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Also of interest is the alkylene -$CH(CH_3)$-.

The terms "cycloalkyl" refers to any cyclic ring of an alkane having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms has been replaced with a halogen (i.e., F, Cl, Br and/or I). Thus, for example, "C_{1-6} haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "C_{4-7} azacycloalkyl" (or "C_4-C_7 azacycloalkyl") means a saturated cyclic ring consisting of one nitrogen and from four to seven carbon atoms (i.e., pyrrolidinyl, piperidinyl, azepanyl, or octahydroazocinyl).

The term "C_{3-6} diazacycloalkyl" (or "C_3-C_6 diazacycloalkyl") means a saturated cyclic ring consisting of two nitrogens and from three to six carbon atoms (e.g., imidazolidinyl, pyrazolidinyl, or piperazinyl).

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, and so forth.

When any variable (e.g., R^a, R^b, or HetA) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "is optionally substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple

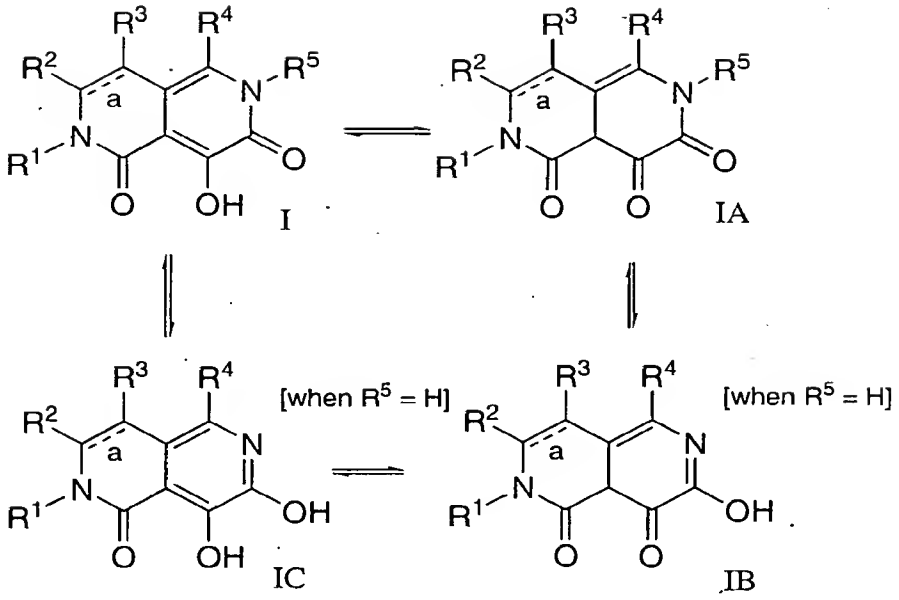
substitution (including multiple substitution at the same site) is chemically allowed. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound.

Any of the various carbocyclic and heterocyclic rings and ring systems defined herein may be attached to the rest of the compound at any ring atom (i.e., any carbon atom or any heteroatom) provided that a stable compound results. Suitable 5- or 6-membered heteroaromatic rings include, for example, pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. The foregoing are representative of heteroaromatics defined by HetB and HetL, and included in the definitions of HetC and HetD. Suitable heteroaryls consisting of an aryl fused with a 5- or 6-membered heteroaromatic ring include, for example, benzopiperidinyl, benzisoxazolyl, benzoxazolyl, chromenyl, quinolinyl, isoquinolinyl, cinnolinyl, and quinazolinyl. The foregoing are representative of fused bicyclic heteroaryls included in the definition of HetC and of fused aryl in part (A) of the definition of R^J. Suitable 4- to 7-membered saturated heterocyclics include, for example, azetidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, azepanyl, diazepanyl, thiadiazinanyl, tetrahydropyranyl, tetrahydrothiopyranyl, and dioxanyl. The foregoing are representative of saturated heterocyclics defined by HetK and included in the definition of HetD.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

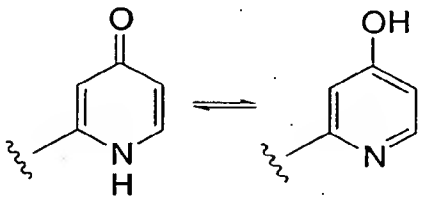
As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers, such as the following:



For the purposes of the present invention a reference herein to a compound of Formula I, II, or III is a reference to the compound per se, or to any one of its tautomers per se, or to mixtures of two or more tautomers.

In instances where a hydroxy (-OH) substituent(s) is(are) permitted on a heteroaromatic ring and keto-enol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the keto form, as exemplified here for a hydroxypyridinyl substituent:



Compounds of the present invention having a hydroxy substituent on a carbon atom of a heteroaromatic ring are understood to include compounds in which only the hydroxy is present, compounds in which only the tautomeric keto form (i.e., an oxo substitutent) is present, and compounds in which the keto and enol forms are both present.

The compounds of the present inventions are useful in the inhibition of HIV integrase (e.g., HIV-1 integrase), the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection

by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or prodrug and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combining the specified ingredients.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV integrase and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HIV integrase, preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the

present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention is also directed to use of the HIV integrase inhibitor compounds of the present invention with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332 or in the Table in WO 02/30930. Suitable HIV/AIDS antivirals for use in combination with the compounds of the present invention include, for example, HIV protease inhibitors (e.g., indinavir, atazanavir, lopinavir optionally with ritonavir, saquinavir, or nelfinavir), nucleoside HIV reverse transcriptase inhibitors (e.g., abacavir, lamivudine (3TC), zidovudine (AZT), or tenofovir), and non-nucleoside HIV reverse transcriptase inhibitors (e.g., efavirenz or nevirapine). It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the foregoing substances or to the list in the above-referenced Tables in WO 01/38332 and WO 02/30930, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. The HIV/AIDS antivirals and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, 57th edition, Thomson PDR, 2003. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

Abbreviations used in the instant specification, particularly the in the Schemes and Examples, include the following:

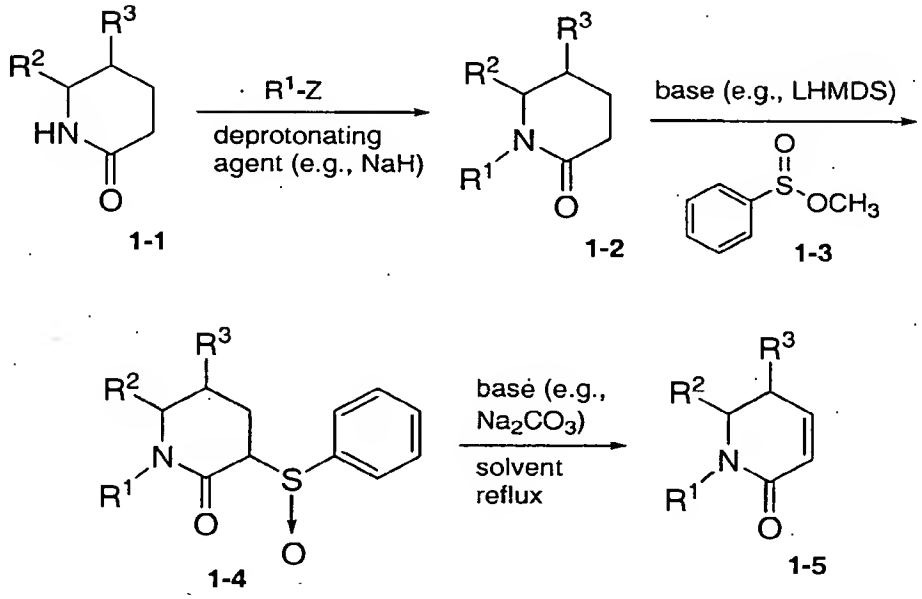
Ac = acetyl
AIDS = acquired immunodeficiency syndrome
AIBN = 2,2-azobisisobutyronitrile
ARC = AIDS related complex
BOP = benzotriazol-1-yloxytris-(dimethylamino)phosphonium
DABCO = 1,4-diazabicyclo[2.2.2]octene
DCM = dichloromethane
DMF = N,N-dimethylformamide
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (or N,N'-dimethylpropyleneurea)
DMSO = dimethylsulfoxide
ES MS = electrospray mass spectroscopy
EtOAc = ethyl acetate
HIV = human immunodeficiency virus
HOAc = acetic acid
HPLC = high performance liquid chromatography
HMPA = hexamethylphosphoramide
IPAc = isopropyl acetate
LC = liquid chromatography
LHMDS = lithium hexamethyldisilazide
mCPBA = meta-chloroperbenzoic acid
Me = methyl
MeOH = methanol
MTBE = methyl tert-butyl ether
NBS = N-bromosuccinimide
NMR = nuclear magnetic resonance
TEA = triethylamine
TFA = trifluoroacetic acid
THF = tetrahydrofuran

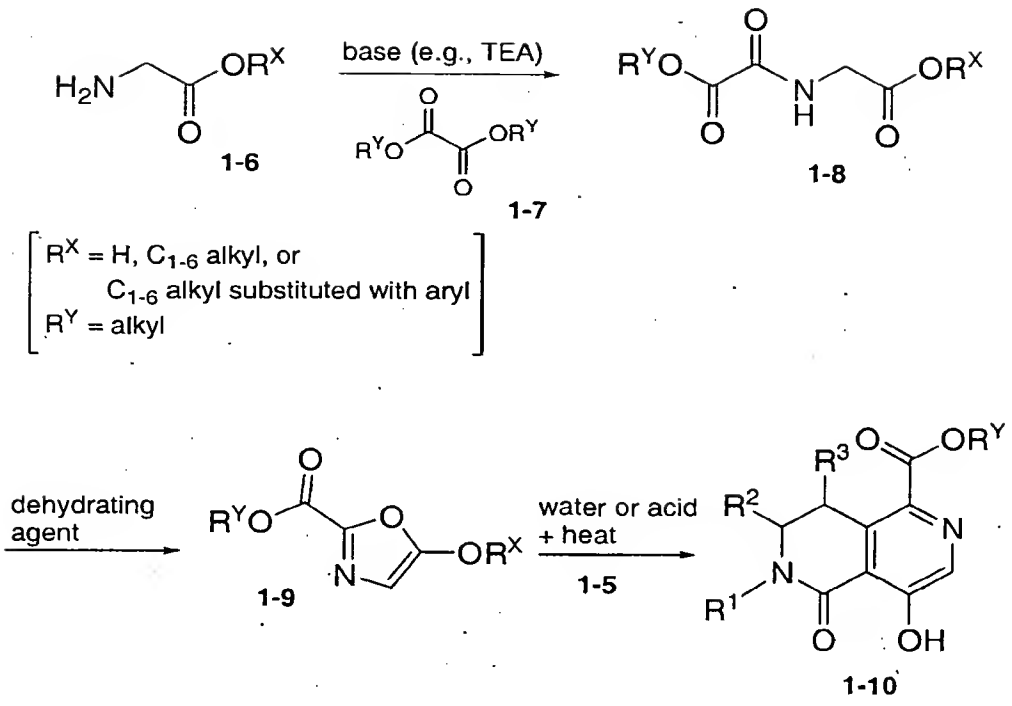
The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make

use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

Scheme 1 depicts a method for preparing 5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate intermediates useful for making compounds of the present invention. In the scheme, lactam **1-1** can be alkylated with an appropriate alkyl halide to give **1-2**, using methods as described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 377-379. Piperidin-2-one **1-2** can be converted to the corresponding dihydropyridinone compound **1-5** following the two step procedure set forth in Meyers et al., *Tett. Lett.* 1995, 36: 7051-7054, wherein the lactam can be treated with base and methyl benzene sulfinate to give intermediate **1-4**, which can then be treated by heating in a high boiling solvent (e.g., toluene) and optionally in the presence of base to effect the elimination to **1-5**. Separately, oxazoles of the type **1-9** can readily be prepared by acylating amino acid ester **1-6** with an oxylate ester **1-7** in the presence of base to afford acylated compound **1-8**, which can then be cyclized and dehydrated (using, e.g., P_2O_5) in the manner described in Krapcho et al. *J. Heterocyclic Chem.* 1995, 32, 1693-1702 to afford oxazole **1-9**. Diels-Alder reaction of **1-9** and **1-5**, optionally in the presence of water or an acid (preferably in the presence of water), will then provide the desired napthyridine intermediate **1-10**.

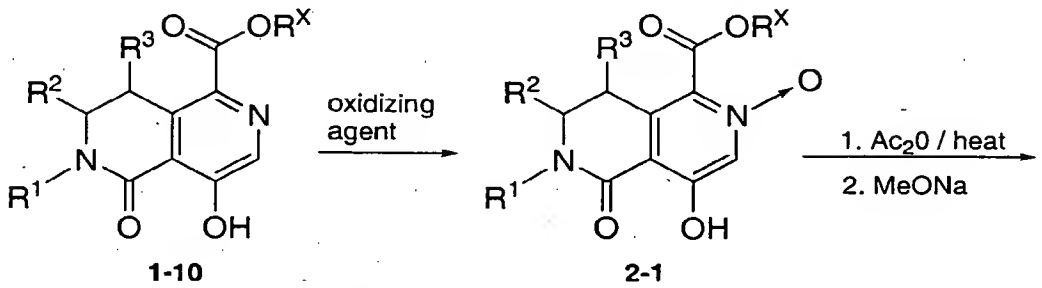
SCHEME 1

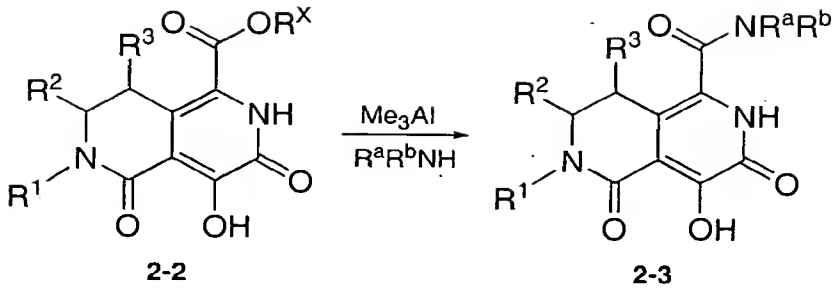




Scheme 2 depicts a method for preparing naphthyridine carboxylates and carboxamides embraced by the present invention from naphthyridine intermediate **1-10**, wherein the intermediate **1-10** is contacted with a suitable oxidizing agent (e.g., hydrogen peroxide or mCPBA) to obtain N-oxide **2-1**, which can then be treated as described Suzuki et al. *J.Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the desired dioxohexahydro-2,6-naphthyridine-1-carboxylate **2-2**. The alkyl carboxylate **2-2** can then be further treated with an appropriate amine and trimethylaluminum in the manner described in Evans et al., *J. Am. Chem. Soc.* 1990, 112: 7001 to give the desired alkyl carboxamide **2-3**.

SCHEME 2

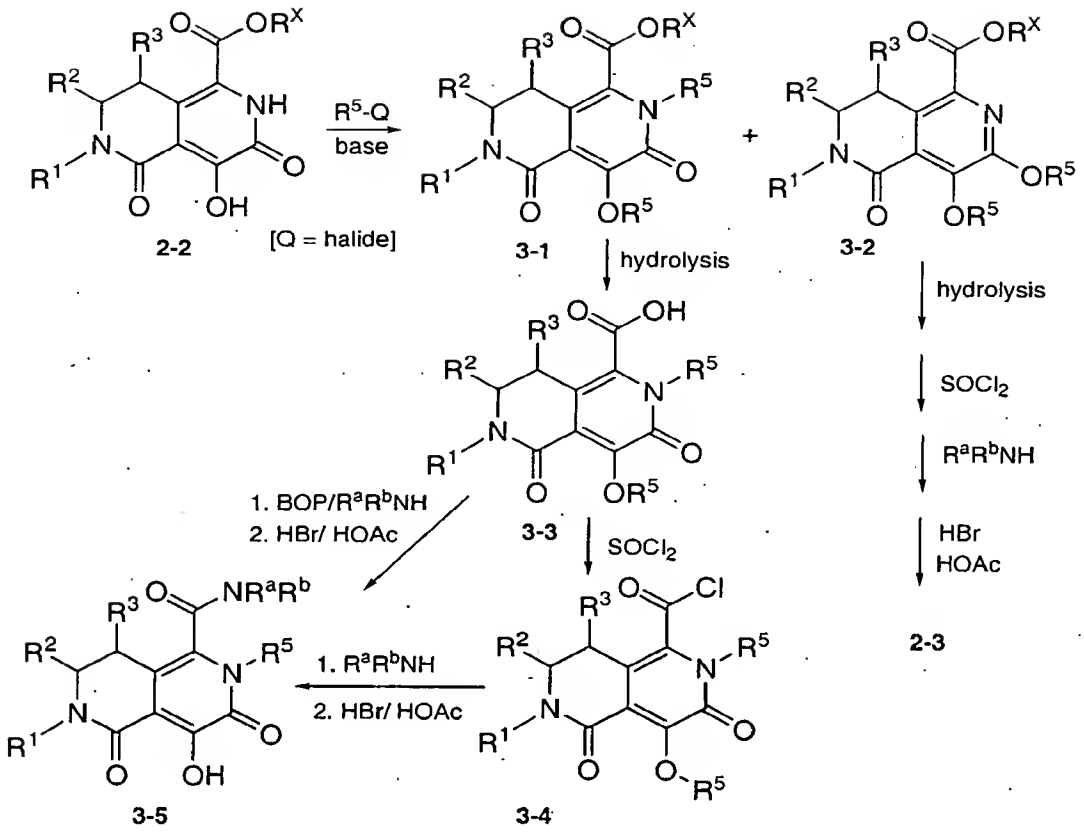




2-2 2-3

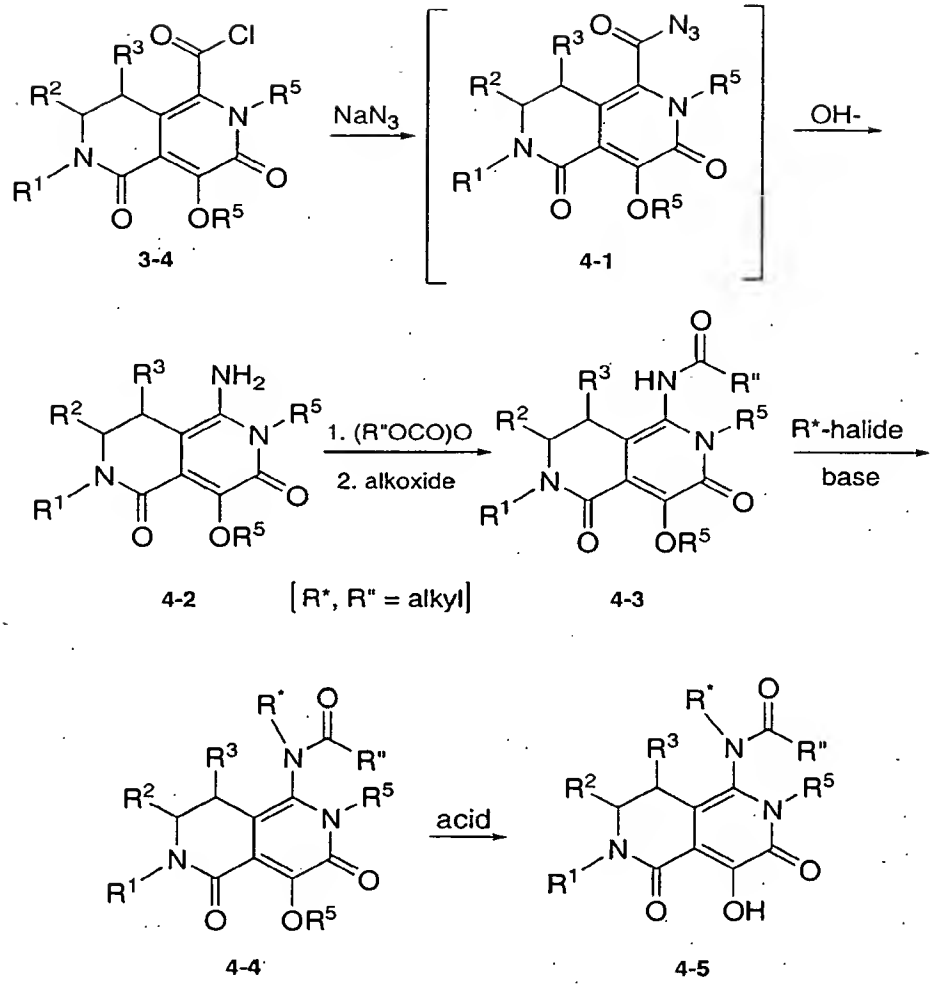
Scheme 3 depicts an alternative method for preparing naphthyridine carboxamides **2-3** and analogs in which the R^5 substituent is other than H. The intermediate **2-2** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., (i) an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, (ii) an alkali metal hydride such as NaH, (iii) a metal alkoxide such as $Mg(OMe)_2$, or (iv) the combination of (i) and (iii) in successive steps) to give a mixture of N- and O-alkylated products **3-1** and **3-2**. A similar method using alkali metal carbonates is described in T. Ukita et.al., *Chem. Pharm. Bull.* 2000, 48 (4): 589-591. Analogs possessing a non-H R^5 substituent can also be prepared by hydrolysis of the N-alkylated product **3-1** with a nucleophile such as hydroxide to afford the acid **3-3**, followed by conversion to the acid chloride **3-4** using a suitable agent like thionyl chloride or oxalyl chloride/catalytic DMF, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 388. The acid **3-3** can be coupled with an amine using a peptide coupling reagent such as BOP, or, alternatively, the acid chloride **3-4** can be treated directly with an amine to give the amide. The O-alkylated groups can then be removed under acidic conditions (e.g., using a strong acid like HBr in a suitable solvent like acetic or propionic acid, or using p-toluene sulfonic acid, or a reagent like BBr_3) to give **3-5**, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 384. A similar sequence of hydrolysis, acid chloride formation, coupling and de-protection, starting from the bis-O-alkylated compound **3-2**, can allow the preparation of compounds **2-3**.

SCHEME 3



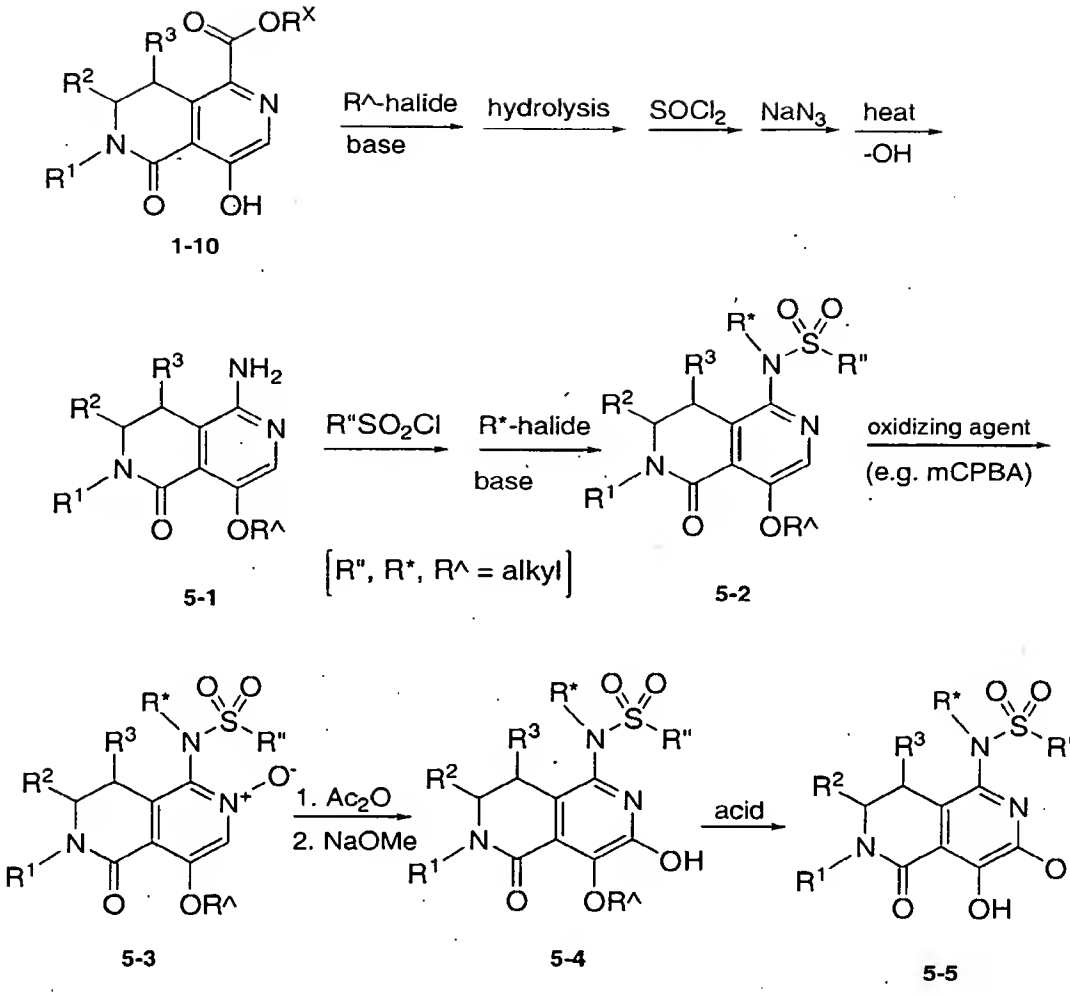
Scheme 4 depicts a method for preparing compounds of the invention in which the R^4 group is linked to the parent template via a nitrogen-carbon bond. Acid chloride 3-4 can be treated with sodium azide to give the acyl azide, which will undergo Curtius rearrangement followed by hydrolysis to the amine **4-2**, similar to the method described in R.J. Borchis et.al. *J. Med. Chem.* (1981), 24, 1518-1521. The amine may then be acylated or sulfonylated with the appropriate agent like an acyl or sulfonyl anhydride or acyl or sulfonyl chloride to give the mono or bis N-acyl or N-sulfonylated intermediate, which can then be converted to product **4-3** by using a suitable nucleophile like sodium methoxide or sodium hydroxide. The amine can further be modified by alkylation with a suitable alkyl halide under the influence of a base (e.g., Cs_2CO_3 or K_2CO_3, using a method similar to that described in A. Nadin, et.al. *J. Org. Chem.* (2003), 68(7), 2844-2852, to give compounds **4-4**. The O-alkyl group can then be removed with a strong acid like HBr to give **4-5**.

SCHEME 4



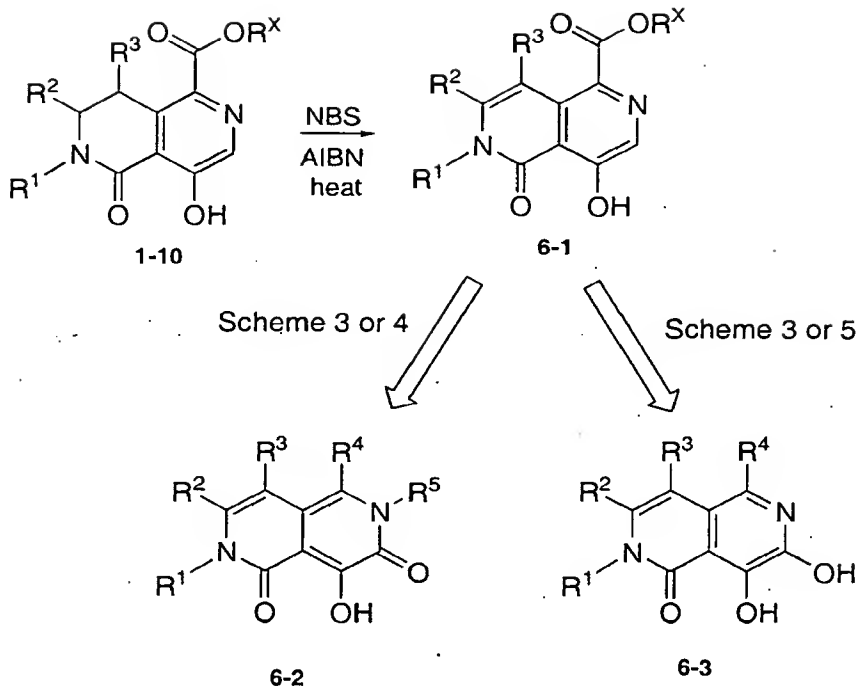
Scheme 5 depicts an alternative sequence of transformations similar to those described in the above schemes. Starting with the intermediate **1-10**, O-alkylation, hydrolysis of the ester to the acid, acid chloride formation, acyl azide formation, Curtius rearrangement and hydrolysis give the intermediate **5-1**, which can be derivatized with various acyl or sulfonyl halides, and then alkylated to give **5-2**. N-oxide formation, similar to that described in M. Adamczyk, *Tetrahedron* (2002) 58, 6951-6963, followed by rearrangement in acetic anhydride and hydrolysis will give **5-4**, and cleavage of the O-alkyl group in acid will afford **5-5**.

SCHEME 5



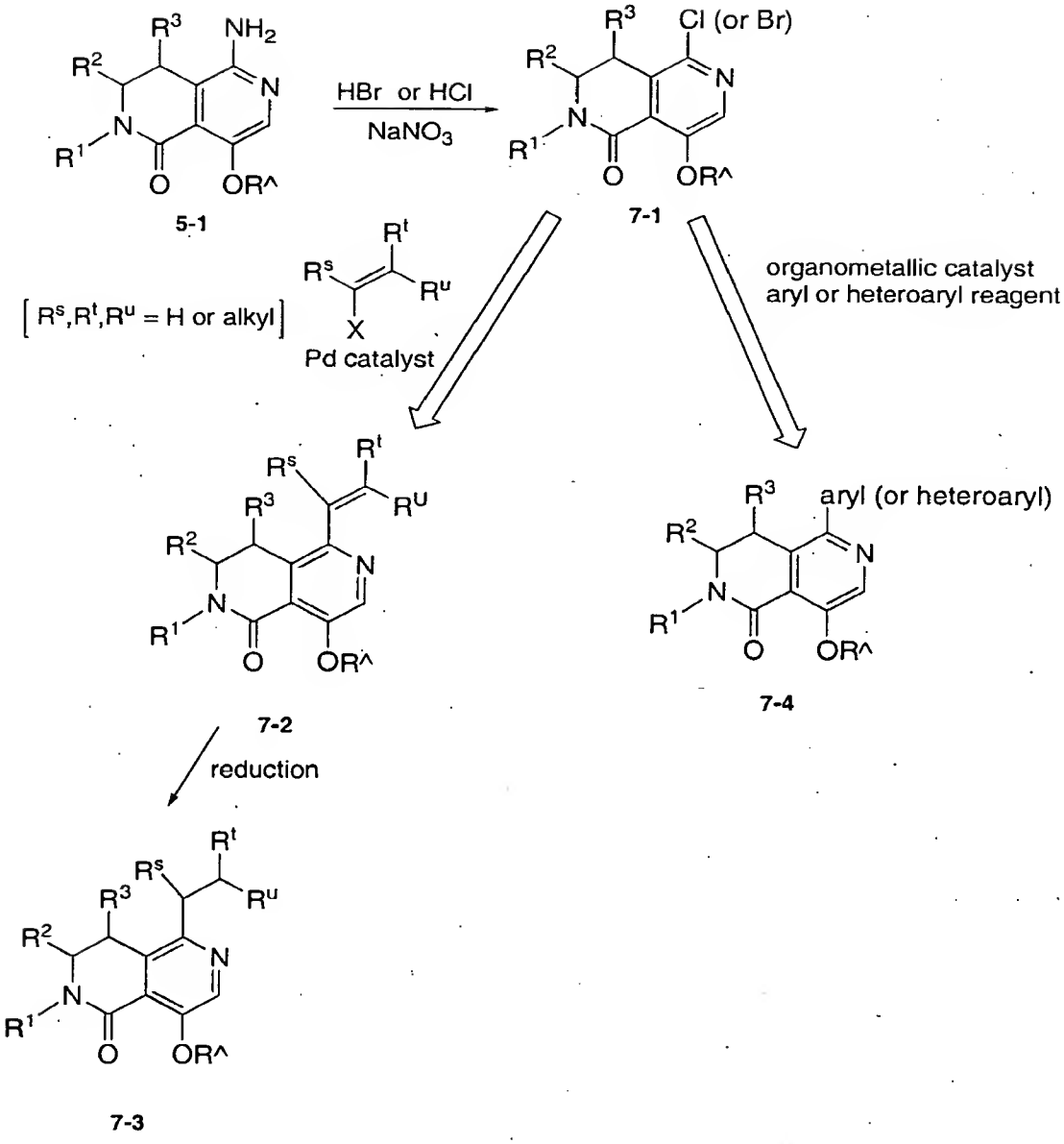
Scheme 6 depicts a route to compounds containing a double bond in the "a" position. These analogs can be prepared from treatment of an intermediate like **1-10** with a brominating agent (e.g., NBS) followed by elimination to give the double bond, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 914. The intermediate **6-1** can then be taken through a series of transformations as previously outlined to give products **6-2** and **6-3**.

SCHEME 6



Scheme 7 shows methods that can be used to prepare analogs in which R^4 is attached by a carbon-carbon bond. The amine **4-2** or **5-1** can be converted to the halide **7-1**, using methods described in A. Bouillon et.al. *Tetrahedron* 58 (14) 2885-2890 (2002), which will allow for carbon-carbon bond formation. Treatment of the halide with a palladium catalyst and vinyl halide, for example, using methods developed by R. F. Heck (M. Schlosser, Organometallics in Synthesis, a Manual 2nd ed. John Wiley and Sons, Ltd. NY 2002, pp 1169) can provide intermediate **7-2**, which can be reduced to the alkyl analog **7-3**. Similarly, treatment of the halide with an organometallic catalyst such as zinc or palladium and an aryl or heteroaryl boronic acid, an aryl or heteroaryl tin reagent, or an aryl and heteroaryl halide will afford the product **7-4** Such transformations are well known in the art and are described, for example, in J.J. Li, G.W.Gribble Palladium in Heterocyclic Chemistry, Pergamon Press NY 2000. Compounds **7-3** and **7-4** can then be taken through the sequence of steps elaborated in previous schemes to afford additional compounds of the present invention.

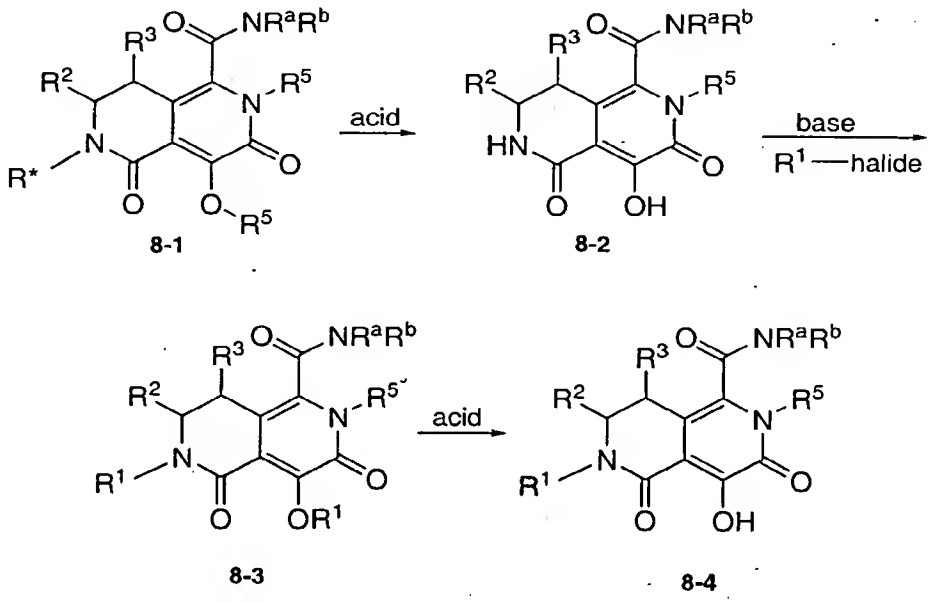
SCHEME 7



Scheme 8 depicts a method for preparing analogs with R^1 substituents from starting substrate **8-1** with a removable R^* group. Substrate **8-1**, containing an R^* functional group (i.e., a group which is readily removable from an amide moiety, such as p-methoxybenzyl, 3,4- or 2,4-bismethoxybenzyl, allyl, or tosyl), can be prepared by coupling a suitable acid **3-3** or acid chloride **3-4** with an amine (see Scheme 3), and can be de-protected with a strong acid like p-toluene sulfonic acid in a manner similar to the method described in W.M. Kan et.al., *Tetrahedron* 2000, 44: 1039-1041 to give

intermediate **8-2**. Deprotected compound **8-2** can then be bis-alkylated with a suitable alkyl halide using a base (e.g., NaH) to give the N,O-alkylated intermediate **8-3**. Removal of the O-alkyl group with strong acid (e.g., HBR in a solvent such as acetic or propionic acid) will then afford the product **8-4**.

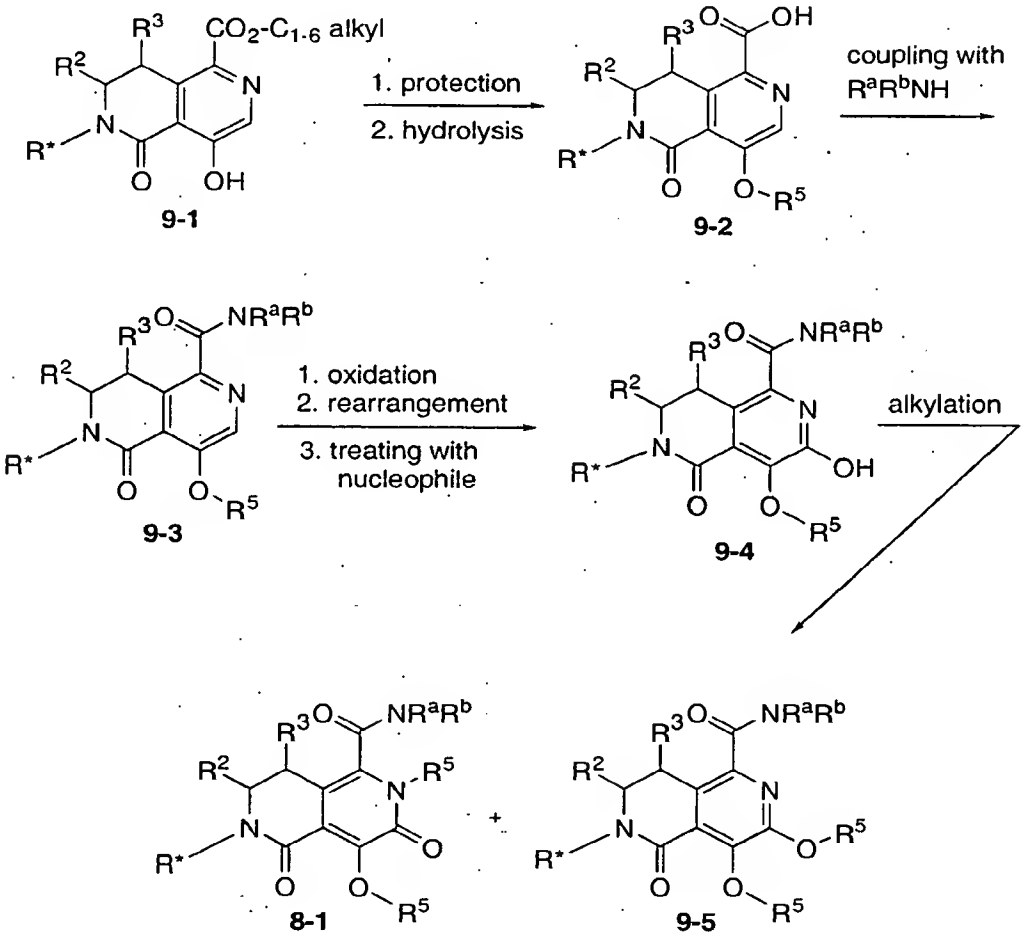
SCHEME 8



Scheme 9 depicts an alternative method for preparing naphthyridine carboxamide analog intermediate **8-1** embraced by the present invention in which the amide substituent is incorporated early in the reaction scheme, and in which the R^* substituent (defined in Scheme 8) is used to allow variation of R^1 at a late stage in the synthesis. Starting material **9-1** can be prepared in a manner similar to that used for **1-10**, incorporating the removable group in the initial alkylation step as described for **1-2**. The phenolic group in **9-1** can be protected with a suitable alkyl protecting group (e.g., an R^5 group as defined herein other than H) followed by hydrolysis with a nucleophile such as hydroxide to afford **9-2**. Protection can be accomplished, for example, by treatment with a diazomethane reagent (e.g., TMS diazomethane) in solvent (e.g., chloroform) or by alkylation with an alkylating agent (e.g., by contact with an alkyl halide or an alkyl sulfate such as dimethyl sulfate) in the presence of a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3 or an alkali metal hydride such as NaH) in a solvent such as DMSO or methylene chloride. The acid **9-2** can be coupled with an amine using a peptide coupling reagent such as EDC to obtain **9-3**. The intermediate **9-3** can then be treated with a suitable oxidizing agent (e.g., mCPBA or peracetic acid) to obtain the N-oxide, which can then be treated as described Suzuki et al. *J. Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the

rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the dioxohexahydro-2,6-naphthyridine-1-carboxylate **9-4**. Intermediate **9-4** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, an alkali metal hydride such as NaH, or a metal alkoxide such as $Mg(OMe)_2$) in a solvent like DMSO to give a mixture of N- and O-alkylated products **8-1** and **9-5**. A similar use of alkali metal carbonates is described in T. Ukita, et.al. *Chem. Pharm. Bull.* 2000, 48 (4) 589-591.

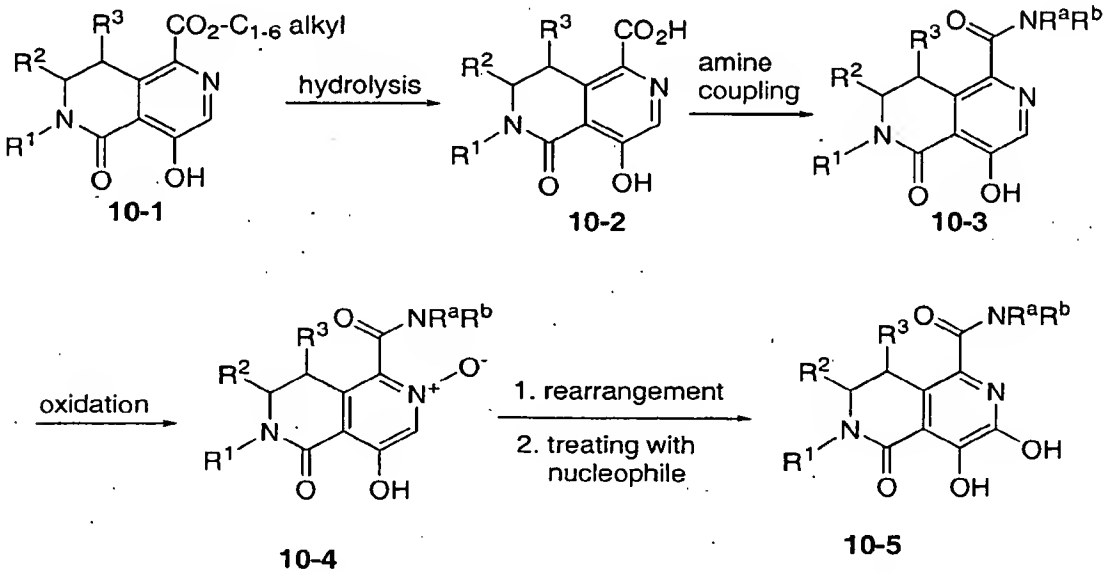
SCHEME 9

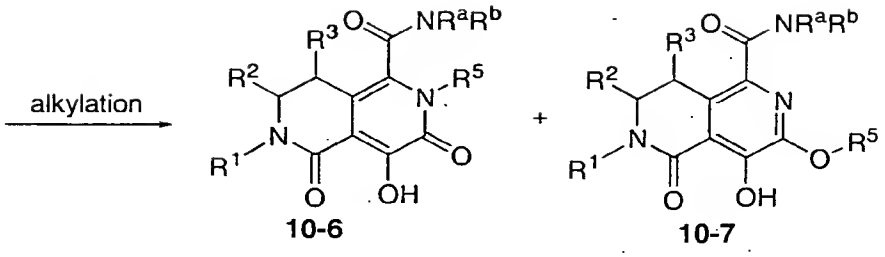


Scheme 10 depicts an alternative method for preparing naphthyridine carboxamide analogs embraced by the present invention in which the R^5 substituent is other than H, starting from naphthyridine intermediate **10-1**. Hydrolysis of the pyridine **10-1** with a nucleophile such as hydroxide

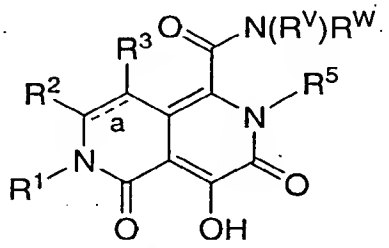
can afford the acid **10-2**, which can be coupled with an amine using a peptide coupling reagent such as BOP to afford amide **10-3**. Alternatively, **10-2** can be converted to the acid chloride using a suitable agent like thionyl chloride or oxalyl chloride/catalytic DMF, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 388, and the acid chloride treated directly with an amine to give the amide **10-3**. The intermediate **10-3** can then be treated with a suitable oxidizing agent (e.g., mCPBA or peracetic acid) to obtain the N-oxide **10-4**, which can then be treated as described Suzuki et al. *J. Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the desired dioxohexahydro-2,6-naphthyridine-1-carboxylate **10-5**. Intermediate **10-5** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, an alkali metal hydride such as NaH, or a metal alkoxide such as $Mg(OMe)_2$)) in a solvent like DMSO to give a mixture of N- and O-alkylated products **10-6** and **10-7**. A similar use of alkali metal carbonates is described in T. Ukita, et.al. *Chem. Pharm. Bull.* 2000, 48 (4) 589-591.

SCHEME 10



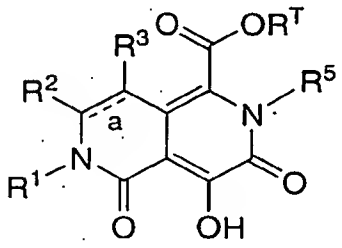


The present invention also includes a process (alternatively referred to herein as "Process P1" or the "P1 process") for preparing a compound of Formula IV:



(IV),

which comprises contacting a compound of Formula V:



(V)

with a Grignard salt of an amine of Formula VI:

$$HN(R^V)R^W \quad (VI)$$

to obtain Compound IV; wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl,

(2) -C_{1-6} alkyl substituted with -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -NO_2, -$N(R^a)R^b$, or -$S(O)_nR^a$,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} alkyl,

(5) halogen,

(6) -$C(=O)N(R^a)R^b$, or

(7) -SO_2R^a, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:

(1) phenyl,

(2) benzyl, or

(3) -HetB;

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl substituted with aryl;

R^2 and R^3 are each independently -H or -C_{1-6} alkyl;

R^5 is:

(1) -C_{1-6} alkyl,

(2) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

(3) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

(4) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} alkyl, or halogen, or

(5) -C_{1-6} alkyl substituted with a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl;

R^T is -C_{1-6} alkyl;

R^V and R^W are each independently -C_{1-6} alkyl or R^V and R^W together with the N atom to which they are both attached form a 4- to 6-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^V and R^W selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, and wherein the saturated heterocyclic ring is optionally substituted with 1 or 2 substituents each of which is independently a C_{1-6} alkyl group;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

Process P1 can produce Compound IV from Compound V in good yield without protecting the 4-hydroxy group. The P1 process is exemplified in Step 8 of Example 20, wherein the protection and deprotection steps included in the process set forth in Example 12 are avoided.

The Grignard salt employed in the P1 process is typically a halomagnesium salt of amine VI. The halomagnesium salt of amine VI is preferably a chloromagnesium salt or a bromomagnesium salt of amine VI, and is more preferably a chloromagnesium salt of amine VI (i.e., $ClMgN(R^V)R^W$).

Representative amines of Formula VI which can be employed in the P1 process include dimethylamine, diethylamine, isopropylethylamine, azetidine, pyrrolidine, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine.

The contacting step of the P1 process is suitably conducted in an aprotic solvent. As used herein, the term "solvent" refers to an organic substance which is a chemically inert liquid under the reaction conditions and which will dissolve or suspend the reactants in such a manner as to bring the reactants into contact and permit the reaction to proceed.

Aprotic solvents suitable for use in the present invention include those selected from the group consisting of alkanes, cycloalkanes, halogenated alkanes, halogenated cycloalkanes, aromatic hydrocarbons, alkylated aromatic hydrocarbons, halogenated aromatic hydrocarbons, alkylated and halogenated aromatic hydrocarbons, ethers, polyalkylphosphoramides, N,N'-dialkylalkyleneureas, and mixtures thereof. In this context, a "halogenated" compound or substance is a compound or substance containing one or more C-H bonds wherein one or more of the hydrogens have been replaced with halogen. A class of solvents suitable for use in the P1 process consists of the solvents selected from the group consisting of C_{1-10} linear and branched alkanes, C_{1-10} linear and branched halogenated alkanes, C_{5-10} cycloalkanes, halogenated C_{5-10} cycloalkanes, benzene, naphthalene, mono- and di- and tri-C_{1-6} alkyl substituted benzenes, halogenated benzenes, halogenated mono- and di- and tri-C_{1-6} alkyl substituted benzenes, dialkyl ethers wherein each alkyl is independently a C_{1-6} alkyl, C_{1-6} linear and branched alkanes substituted with two -O-C_{1-6} alkyl groups (which are the same or different), C_4-C_8 cyclic ethers and diethers, phenyl C_{1-4} alkyl ethers, diethylene glycol di(C_{1-4} alkyl) ethers, hexa (C_{1-6} alkyl)phosphoramides, N,N'-di-(C_{1-6} alkyl)ethyleneureas, and N,N'-di-(C_{1-6} alkyl)propyleneureas.

Representative examples of aprotic solvents suitable for use as a solvent in the P1 process include the following: pentane (individual isomers and mixtures thereof), hexane (individual isomers and mixtures thereof), heptane (individual isomers and mixtures thereof), cyclopentane, cyclohexane, cycloheptane, carbon tetrachloride, chloroform, methylene chloride, 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, chlorocyclopentane, chlorocyclohexane, benzene, toluene, o- and m- and p-xylene, xylene mixtures, ethylbenzene, chlorobenzene, bromobenzene, o-chlorotoluene, 2,4-dichlorotoluene, 2,4,6-trichlorotoluene, ethyl ether, MTBE, THF, dioxane, 1,2-dimethoxyethane, HMPA, and DMPU.

In one embodiment of the P1 process, the contacting comprises adding Compound V to the Grignard salt of amine VI dissolved or suspended in the aprotic solvent to form a reaction mixture and ageing the reaction mixture. The Grignard salt can be prepared, for example, by adding amine VI dissolved or suspended in a first aprotic solvent to a solution of an alkylmagnesium halide (e.g., a C_{1-4} alkylmagnesium chloride or bromide) in a second aprotic solvent that is the same or different from the first aprotic solvent. The addition can suitably be conducted with agitation (e.g., stirring) at a temperature at or below about 0°C (e.g., from about -50 to about 0°C, or from about -10 to about 0°C). The resulting admixture (either a solution or suspension) can then be aged with agitation for a time

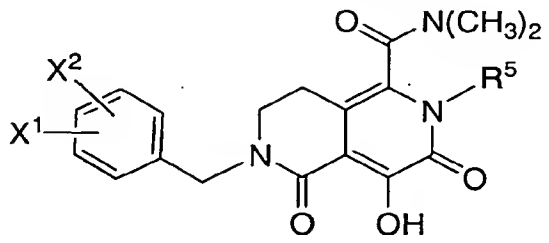
sufficient to effect formation of the amine salt, after which Compound V, typically dissolved or suspended in a third aprotic solvent that is the same or different from the first and second solvents, can be charged to the admixture (either maintained at a temperature below about 0°C -- e.g., from about -10 to about 0°C -- or warmed to a temperature in a range of from about 0 to about 25°C) to provide a reaction mixture, and the resulting reaction mixture is aged until the desired degree of conversion of Compound V is achieved or until conversion is complete.

As used herein, the term "ageing" and variants thereof (e.g., "aged") refer to maintaining the reactants in a given reaction or treatment step in contact for a time and under conditions effective for achieving the desired degree of conversion.

Process P1 can be conducted at any temperature at which the reaction forming Compound IV can be detected. The reaction (i.e., the contacting) can suitably be conducted at a temperature in a range of from about -40 to about 40°C, is typically conducted at a temperature in a range of from about -20 to about 25°C, and is more typically conducted at a temperature in a range of from about -10 to about 0°C.

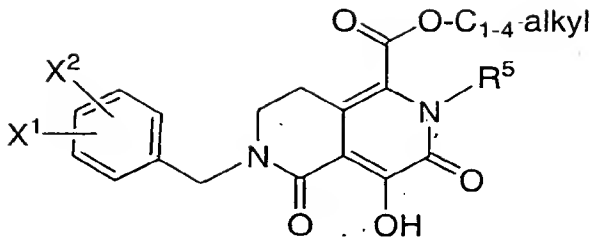
The Grignard salt of amine VI can be employed in any proportion with respect to Compound V which results in the formation of at least some of the desired compound of Formula IV, but the Grignard salt is typically employed in a proportion which, under the reaction conditions (e.g., temperature) employed, can optimize conversion of Compound V to Compound IV. The Grignard salt is suitably employed in an amount in a range of at least about 2 equivalents (e.g., from about 2 to about 10 equivalents) per equivalent of Compound V, is typically employed in an amount in a range of from about 3 to about 6 equivalents per equivalent of Compound V, and is more typically employed in an amount in a range of from about 4 to about 5 equivalents per equivalent of Compound V.

An embodiment of the P1 process is the process as originally defined above, wherein the compound of Formula IVis a compound of Formula IV-A:



(IV-A);

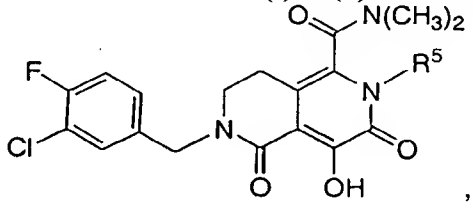
the compound of Formula V is a compound of Formula V-A:

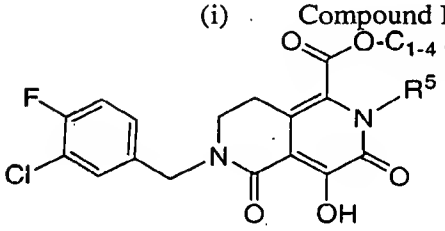


(V-A);

the Grignard salt is a Grignard salt of dimethylamine; X^1 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy; X^2 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methyl, (6) methoxy, (7) $-CF_3$, or (8) $-OCF_3$; and R^5 is $-C_{1-4}$ alkyl.

Additional embodiments of the P1 process include the process as just described in the preceding embodiment incorporating one or more of the features (i) to (v) as follows:

(i) Compound IV-A is 

, and Compound V-A is 

;

(ii) the contacting is conducted in an aprotic solvent selected from the group consisting of an alkane, a cycloalkane, a halogenated alkane, a halogenated cycloalkane, an aromatic hydrocarbon, an alkylated aromatic hydrocarbon, a halogenated aromatic hydrocarbon, an alkylated and halogenated aromatic hydrocarbon, an ether, a polyalkyl phosphoramide, an N,N'-dialkylalkyleneurea, and mixtures thereof;

(iii) the Grignard salt is $ClMg(CH_3)_2$;

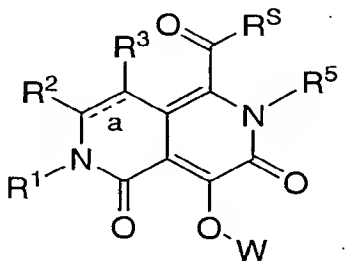
(iv) the contacting is conducted at a temperature in a range of from about -20 to about 25°C (e.g., in a range of from about -10 to about 0°C); and

(v) the Grignard salt is employed in an amount of at least about 2 equivalents (e.g., in an amount in a range of from about 2 to about 10 equivalents, or from about 3 to about 6 equivalents, or from about 4 to about 5 equivalents) per equivalent of Compound V-A.

Another embodiment of Process P1 is the process as originally set forth above or as described in a preceding embodiment, which further comprises recovering Compound IV from the reaction medium. Compound IV can be recovered, for example, by quenching the reaction mixture with

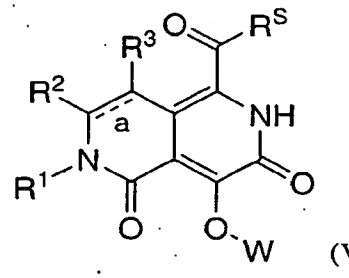
an aqueous solution of a mineral acid (e.g., aqueous HCl), separating the resulting organic layer (i.e., the aprotic solvent medium containing the desired product), and removing in whole or in part the volatile solvent from the organic layer using heat or a vacuum or both to obtain Compound IV either directly or by precipitation from the concentrated organic layer and separation of the precipitate by filtration.

The present invention also includes a process (alternatively referred to herein as "Process P2" or the "P2 process") for preparing a compound of Formula VII:



(VII)

which comprises reacting an alkylating agent of formula R^5-Z with a compound of Formula VIII:



(VIII)

in a polar aprotic solvent and in the presence of a base selected from a magnesium base and a calcium base; wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

W is -H or -C_{1-6} alkyl;

Z is halogen or -SO_3-Q wherein Q is (i) C_{1-6} alkyl or (ii) phenyl optionally substituted with 1 or 2 substituents each of which is independently a C_{1-6} alkyl;

R^S is -O-C_{1-6} alkyl or $N(R^V)R^W$ wherein R^V and R^W are each independently -C_{1-6} alkyl or R^V and R^W together with the N atom to which they are both attached form a 4- to 6-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^V and R^W

selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, and wherein the saturated heterocyclic ring is optionally substituted with 1 or 2 substituents each of which is independently a C_{1-6} alkyl group;

R^5 is:

(1) -C_{1-6} alkyl,

(2) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

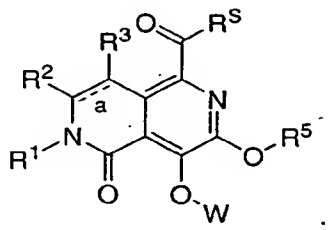
(3) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

(4) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} alkyl, or halogen, or

(5) -C_{1-6} alkyl substituted with a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl;

and R^1, R^2, and R^3 are each independently as originally defined above.

Compounds embraced by Formula VII include compounds of the present invention (i.e., when W is H) and compounds which can be used as intermediates (i.e., when W is C_{1-6} alkyl) in the preparation of compounds of the present invention. The use of a magnesium base or a calcium base (preferably a magnesium base) can favor the desired N-alkylation over O-alkylation; e.g., the formation of a compound of Formula VII over the formation of the following compound:



The base employed in Process P2 can be a magnesium-containing base or a calcium-containing base. Magnesium and calcium bases suitable for use in the process include those of formula $M(R^X)_2$, wherein M is Mg or Ca, and each R^X is independently H or -O-C_{1-6} alkyl. Exemplary bases

include MgH_2, $Mg(OMe)_2$, $Mg(OH)_2$, $Mg(OEt)_2$, MgHOMe, MgHOEt, CaH_2, $Ca(OMe)_2$ and $Ca(OEt)_2$. The base is preferably a magnesium base. In one embodiment, the P2 process is as originally set forth above, wherein the base comprises a magnesium base of formula $Mg(R^X)_2$ where R^X is as defined above. In an aspect of this embodiment, the base is a $Mg(O\text{-}C_{1\text{-}4}\text{-}\ alkyl)_2$. In another aspect of this embodiment, the base is $Mg(OMe)_2$.

The base can be employed in any proportion with respect to Compound VIII and alkylating agent (e.g., alkyl halide) which results in the formation of at least some of the desired N-akylated compound of Formula VII, but the base is typically employed in a proportion which, under the reaction conditions (e.g., temperature) employed, can optimize conversion of Compound VIII to Compound VII. The base is suitably employed in an amount in a range of from about 0.5 to about 10 equivalents per equivalent of Compound VIII, is typically employed in an amount in a range of from about 1 to about 10 equivalents per equivalent of Compound VIII, and is more typically employed in an amount in a range of from about 1 to about 5 equivalents (e.g., from about 1.5 to about 2 equivalents) per equivalent of Compound VIII.

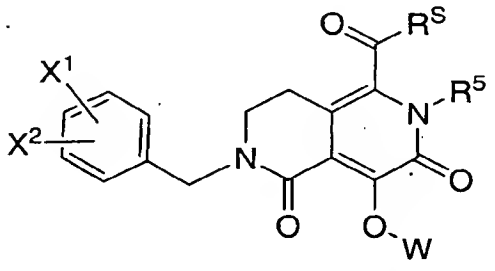
The alkylating agent employed in Process P2 is of formula R^5-Z, wherein R^5 is as defined above and Z is halogen (i.e., F, Cl, Br, or I) or $-SO_3$-Q wherein Q is (i) $C_{1\text{-}6}$ alkyl or (ii) phenyl optionally substituted with 1 or 2 substituents each of which is independently a $C_{1\text{-}6}$ alkyl. In one embodiment, the P2 process is as originally set forth above or as set forth in a preceding embodiment, wherein the alkylating agent is of formula R^5-Z, wherein R^5 is $C_{1\text{-}6}$ alkyl and Z is chloride, bromide, iodide, mesylate, or tosylate. In an aspect of this embodiment, Z is iodide or tosylate. In another aspect of this embodiment, the alkylating agent is MeI or methyl tosylate, and in a feature of this aspect the alkylating agent is methyl tosylate.

The alkylating agent can be employed in any proportion with respect to the base and Compound VIII which results in the formation of at least some of the desired N-akylated compound of Formula VII, but the alkylating agent is typically employed in a proportion which, under the reaction conditions (e.g., temperature) employed will optimize conversion of Compound VIII to Compound VII. The alkylating agent is suitably employed in an amount in a range of from about 0.5 to about 20 equivalents per equivalent of Compound VIII, and is typically employed in an amount in a range of from about 1 to about 20 equivalents per equivalent of Compound VIII. The alkylating agent (e.g., alkyl halide) is more typically employed in an amount in a range of from about 1 to about 10 equivalents (e.g., from about 1 to 5 equivalents) per equivalent of Compound VIII. The alkylating agent is preferably employed in excess with respect to Compound VIII, such as in an amount in a range of from about 2 to about 6 equivalents (e.g., from about 3 to about 5 equivalents, or about 4 equivalents) per equivalent of Compound VIII.

The solvent employed in Process P2 can be any polar aprotic solvent which under the conditions employed is in the liquid phase, is chemically inert, and will dissolve, suspend, and/or disperse the reactants so as to bring them into contact and permit the formation of the desired Compound VII. The solvent is preferably one which under the conditions employed in the process favors N-alkylation to the desired Compound VII over O-alkylation to an O-alkylated by-product. The polar aprotic solvent is suitably a halogenated alkane, an ether, an ester, a tertiary amide, an N-alkylpyrrolidone, a sulfoxide, or a nitrile; and is typically a tertiary amide, an N-alkylpyrrolidone, or a sulfoxide. In one embodiment, the P2 process is as originally set forth above or as set forth in a preceding embodiment, wherein the polar aprotic solvent comprises a N,N-di-(C_{1-6} alkyl)-C_{1-6} alkylamide, a N-(C_{1-6} alkyl)pyrrolidone, or a di-(C_{1-6} alkyl)sulfoxide. In an aspect of this embodiment, the polar aprotic solvent comprises a N,N-di-(C_{1-3} alkyl)-C_{1-3} alkylamide, a N-(C_{1-3} alkyl)pyrrolidone, or a di-(C_{1-3} alkyl)sulfoxide. In another aspect of this embodiment, the polar aprotic solvent is DMF, DMAC, N-methylpyrrolidone, N-ethylpyrrolidone, or DMSO. In a feature of this aspect, the polar aprotic solvent is DMF.

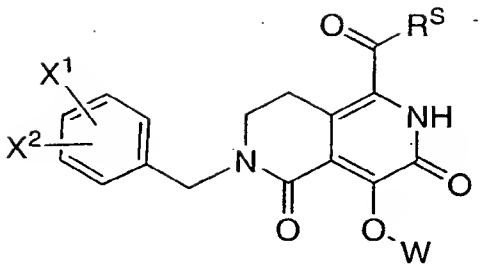
Process P2 can be conducted at any temperature at which the reaction (N-alkylation) forming Compound VII can be detected. The reaction can suitably be conducted at a temperature in a range of from about -20 to about 100°C, is typically conducted at a temperature in a range of from about 0 to about 100°C, and is more typically conducted at a temperature in a range of from about 15 to about 80°C. In one embodiment of the P2 process the temperature is in a range of from about 20 to about 60°C, wherein the process step is initially conducted at about 20°C and subsequently heated to a temperature of about 60°C.

An embodiment of the P2 process is the process for preparing a compound of Formula VII-A:



(VII-A)

which comprises reacting an alkylating agent of formula R^5-Z with a compound of Formula VIII-A:



(VIII-A);

in a polar aprotic solvent and in the presence of a magnesium base; wherein:

W is -H or -C_{1-6} alkyl;

X^1 and X^2 are each independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} alkyl,
(5) halogen,
(6) -CN,
(7) -C(=O)NH_2,
(8) -C(=O)NH(-C_{1-4} alkyl),
(9) -C(=O)N(-C_{1-4} alkyl)$_2$, or
(10) -SO_2-C_{1-4} alkyl;

Z is -Cl, -Br, -I, or tosylate;

R^S is -O-C_{1-6} alkyl or $N(R^V)R^W$ wherein R^V and R^W are each independently -C_{1-6} alkyl; and

R^5 is -C_{1-6} alkyl.

Additional embodiments of the P2 process include the process as just described in the preceding embodiment incorporating one or more of the features (i) to (vi) as follows:

(i) the magnesium base comprises MgH_2 or Mg(O-C_{1-3} alkyl)$_2$ (or is Mg(OMe)$_2$);

(ii) the polar aprotic solvent is a N,N-di-(C_{1-3} alkyl)-C_{1-3} alkylamide, a N-(C_{1-3} alkyl)pyrrolidone, or a di-(C_{1-3} alkyl)sulfoxide (e.g., the solvent is DMF, DMAC, N-methylpyrrolidone, N-ethylpyrrolidone, or DMSO; or the solvent is DMF);

(iii) the reaction is conducted at a temperature in a range of from about 0 to about 100 °C (or from about 20 to about 60 °C);

(iv) the alkylating agent R^5-Z is a C_{1-4} alkyl iodide or a C_{1-4} alkyl tosylate (or is MeI or methyl tosylate);

(v) the alkylating agent R^5-Z is employed in an amount in a range of from about 1 to about 5 equivalents (or from about 3 to about 5 equivalents) per equivalent of Compound VIII-A; and

(vi) the magnesium base is employed in an amount in a range of from about 1 to about 5 equivalents (or from about 1.5 to about 2 equivalents) per equivalent of Compound VIII-A).

Another embodiment of Process P2 is the process as originally set forth above or as described in a preceding embodiment, which further comprises recovering Compound VII from the reaction medium. Process P2 can result in the formation of O-alkylated by-product, which can be separated from the desired N-alkylated product (i.e., Compound VII) by methods known in the art such as washing the precipitated solids with suitable solvents or via chromatography.

It is understood that tautomers can exist for Compound IV and Compound V in Process P1 and Compound VII and Compound VIII in Process P2 as a result of keto-enol tautomerism. The P1 and P2 processes encompass all tautomeric forms, individually and in mixtures.

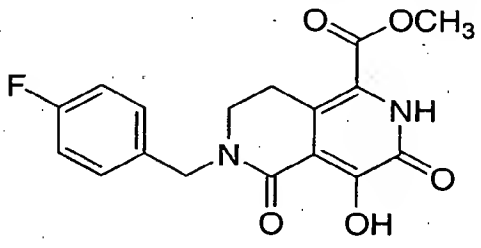
The progress of any reaction step of any chemical process set forth herein, including processes P1 and P2, can be followed by monitoring the disappearance of a reactant (e.g., Compound VIII) and/or the appearance of the desired product (e.g., Compound VII) using such analytical techniques as TLC, HPLC, IR, NMR or GC.

Unless a contrary meaning is clear from the context, a reference herein to "equivalent" or "equivalents" means molar equivalent(s).

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

Methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate



Step 1: 1-(4-Fluorobenzyl)piperidine-2-one

To a suspension of sodium hydride (2.4 g, 0.1 mol) in anhydrous THF (400 mL) was added piperidine-2-one (9.0 g, 90 mmol) in anhydrous THF (20 mL) over 10 minutes. After 20 minutes, the resultant thick slurry was treated with 4-fluorobenzyl bromide (18.9 g, 99.9 mmol). The reaction mixture was refluxed overnight. The resultant mixture was cooled to 0 °C and treated with H_2O (10 mL) cautiously. The mixture was stirred for 10 minutes and concentrated under vacuum. The residue was partitioned between ethyl acetate (300 mL) and H_2O. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was subjected to column chromatography on silica gel eluting with 50 % - 70 % ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to afford the benzylated piperidinone as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J*= 8.7 Hz, 5.4 Hz, 2H), 7.00 (t, *J*=8.7 Hz, 2H), 4.56 (s, 2H), 3.18 (t, *J*=6 Hz, 2H), 2.46 (t, *J*=6 Hz, 2H), 1.79 (m, 4H).

Step 2: 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one

To a cooled (0 °C) solution of 1-(4-fluorobenzyl)piperidine (5.0g, 24.1 mmol) in anhydrous THF (100 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 53 mL, 53 mmol) dropwise, and the solution was stirred for one half hour. The solution was treated with methyl benzene sulfinate (5.65g, 36.1 mmol) in anhydrous THF (3 mL) dropwise. After 30 minutes at 0 °C, the resultant mixture was quenched with water and partitioned between 10% $KHSO_4$ and $CHCl_3$, the layers separated and the aqueous extracted several more times with $CHCl_3$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to afford 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one as a waxy solid that was taken on to the next step. ES MS M+1 = 332

Step 3: 1-(4-Fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one

To a solution of 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one (0.37 g, 1.11 mmol) in toluene (15 mL) was added solid Na_2CO_3 (2g, 18.8 mmol). The reaction mixture was refluxed for about 6 hours. The resultant solution was filtered and concentrated under vacuum and the residue chromatographed on silica eluting with a gradient of 0-40% EtOAc/Hexanes to give the product as colorless glass.
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.01 (m, 2H), 6.56 (dt, *J*=9.9 Hz, 4.2 Hz, 1H), 6.00 (dt, *J*=9.7 Hz, 1.8 Hz, 1H), 4.59 (s, 2H), 3.32 (t, *J*=7.2 Hz, 2H), 2.33 (m, 2H).

Step 4: Methyl[(2-methoxy-2-oxoethyl)amino](oxo)acetate

To a cooled (0 °C) solution of the glycine methyl ester (30.0 g, 0.24 mol) in methylene chloride (500 mL) was added triethylamine (50.8 g, 0.50 mol). Methyl oxalyl chloride (29.3 g, 0.24 mol)

was carefully added dropwise. The reaction solution warmed to room temperature and stirred overnight. The product mixture was partitioned between H_2O and methylene chloride. The organic extract was dried with Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.59 (br, 1H), 4.14 (d, *J*=5.6 Hz, 2H), 3.93 (s, 3H), 3.79 (s, 3H). ES MS M+1 = 176

Step 5: Methyl 5-methoxy-1, 3-oxazole-2-carboxylate

To a warm (35 - 40 °C) suspension of phosphorous pentoxide (77.7 g, 109 mmol) in anhydrous acetonitrile (200 mL) was added methyl[(2-methoxy-2-oxoethyl)amino](oxo)acetate (19.19 g, 109.6 mmol). The reaction mixture was heated to 65 °C, then stirred overnight at room temperature. The product mixture was cooled to 0 °C and carefully quenched with ice and brine keeping the reaction from generating an unsuitable exotherm. The resultant mixture was extracted with ethyl acetate (600 mL). The organic extract was washed with brine, dried with Na_2SO_4, then concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 100 % CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the title compound as a light yellow solid that was used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H). ES MS M+1 =158

Step 6: Methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

In a sealed tube, 1-(4-fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one (3.84 g, 18.7 mmol), and methyl 5-methoxy-1,3-oxazole-2-carboxylate prepared in Step 5 (2.94 g, 18.7 mmol), were combined. The reaction mixture was heated at 120 °C. After 24 hours, the resultant mixture was cooled and methanol saturated with HCl (2 mL) was added. The product mixture stirred at room temperature for 40 minutes, then was concentrated under vacuum. The residual crude material was diluted with DMSO (6.0 mL) and filtered to give the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (br, 1H), 8.39 (s, 1H), 7.31 (m, 2H), 7.06 (t, *J*=8.5 Hz, 2H), 4.72 (s, 2H), 3.94 (s, 3H), 3.50 (m, 4H). ES MS M+1 =331

Step 7: Methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

To a solution of methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (0.509 g, 1.541 mmol) in acetic acid (2 mL) was added hydrogen peroxide (35 % wt % in H_2O, 0.262 g, 7.705 mmol). The reaction mixture was heated to 100 °C for 1 hour. The

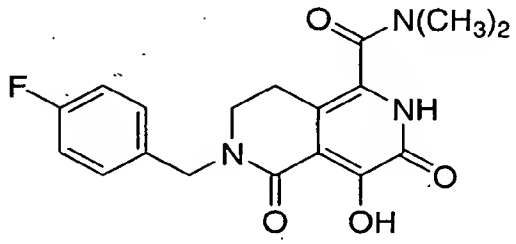
product mixture was concentrated under vacuum and purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a yellow solid. ^{1}HNMR (400 MHz, CD_3OD) δ 7.95 (s, 1H), 7.38 (dd, *J*=5.3 Hz, 8.6 Hz, 2H), 7.08 (t, *J*=8.8 Hz, 2H), 4.71 (s, 2H), 3.93 (s, 3H), 3.56 (t, *J*=6.7 Hz, 2H), 2.89 (t, *J*=6.7 Hz, 2H). ES MS M+1 = 347

Step 8: Methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (0.178 g, 0.514 mmol) was added acetic anhydride (0.157 g, 1.542 mmol) and refluxed. After 1 hour, the reaction mixture was concentrated under vacuum, then sodium methoxide (30 wt. % in methanol, 0.083 g, 1.540 mmol) was added. After stirring at room temperature for 1 hour, the product mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a pale yellow solid.
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.3 Hz, 8.4 Hz, 2h), 7.06 (t, *J*=8.5 Hz, 2H), 4.71 (s, 2H), 3.93 (s, 3H), 3.46 (t, *J*=6.5 Hz, 2H), 3.32 (t, *J*=6.5 Hz, 2H).
ES MS M+1 = 347

EXAMPLE 2

6-(4-Fluorobenzyl)-4-hydroxy-*N*,*N*-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



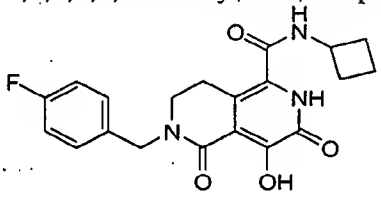
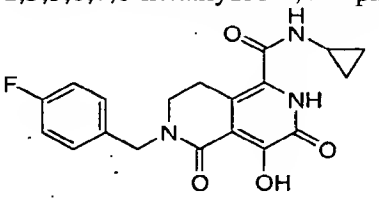
To a cooled (-10 °C) solution of dimethylamine (2M in THF, 0.002 g, 0.035 mmol) was slowly added trimethylaluminum (2M in toluene, 0.002 g, 0.035 mmol) and stirred for 30 minutes at room temperature. The reaction mixture was cooled to -10 °C and methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.004 g, 0.012 mmol, example 1 step 8) in THF (5 mL) was added. The reaction stirred at room temperature for 2 hours, then transferred via syringe to a solution of 1:1 CH_2Cl_2:0.5 N aq. HCl at 0 °C and stirred for 1 hour. The product mixture was separated, and the aqueous was extracted three times with CH_2Cl_2. The aqueous layer was treated

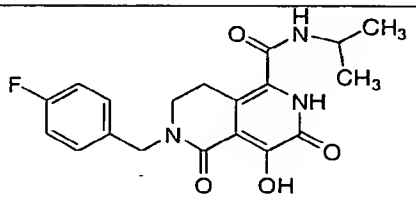
with saturated Na_2CO_3 solution to pH 5 and extracted three times with CH_2Cl_2 again. The organic combined extracts were dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a light yellow solid.

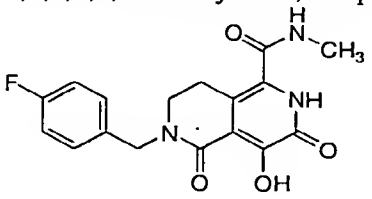
^1H NMR (400 MHz, CD_3OD) δ 7.39 (dd, *J*= 5.3 Hz, 8.6 Hz, 2H), 7.09 (t, *J*=8.8 Hz, 2H), 4.74 (s, 2H), 3.50 (t, *J*=6.4 Hz, 2H), 3.05 (s, 3H), 2.96 (s, 3H), 2.67 (t, *J*=6.4 Hz, 2H) ppm. ES MS M+1 = 360

EXAMPLES 3 - 6

The compounds in the following table were prepared in accordance with the procedure set forth in Example 2 using the appropriate analogous starting materials.

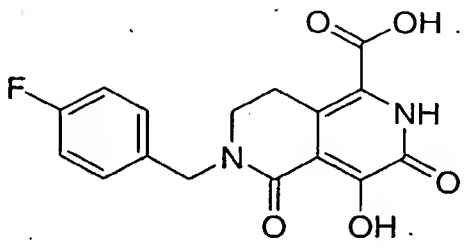
Example	Compound	Data
3	*N*-Cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, CD_3OD) δ 7.39 (dd, *J*=5.6 Hz, 8.7 Hz, 2H), 7.09 (t, *J*=8.7 Hz, 2H), 4.74 (s, 2H), 4.39 (p, *J*=7.9 Hz, 1H), 3.49 (t, *J*=6.1 Hz, 2H), 3.06 (t, *J*=6.1 Hz, 2H), 2.32 (m, 2H), 2.04 (m, 2H), 1.78 (m, 2H) ppm. ES MS M+1 = 386
4	*N*-Cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, $CDCl_3$) δ 13.53 (br, 1H), 7.63 (br, 1H), 7.30 (dd, *J*=5.6 Hz, 8.5 Hz, 2H), 7.06 (t, *J*=8.5 Hz, 2H), 4.71 (s, 2H), 3.51 (m, 2H), 3.46 (m, 2H), 2.86 (m, 1H), 1.88 (br, 1H), 0.83 (q, *J*=5.9 Hz, 2H), 0.71 (m, 2H) ppm. ES MS M+1 = 372
5	6-(4-Fluorobenzyl)-4-hydroxy-*N*-isopropyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.7 Hz, 8.8 Hz, 2H), 7.06 (t, *J*=8.8 Hz, 2H), 6.89 (d,

		*J*=7.3 Hz, 1H), 4.82 (br, 1H), 4.71 (s, 2H), 4.17 (m, 1H), 3.47 (t, *J*=6.3 Hz, 2H), 3.35 (t, *J*=6.3 Hz, 2H), 1.26 (d, *J*=6.1 Hz, 6H) ppm. ES MS M+1 = 374

6	6-(4-fluorobenzyl)-4-hydroxy-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.08 (m, 2H), 4.73 (s, 2H), 3.48 (t, J = 6.6 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H), 2.85 (s, 3H) ppm. MS m/z 346.3 (M +1).

EXAMPLE 7

6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid



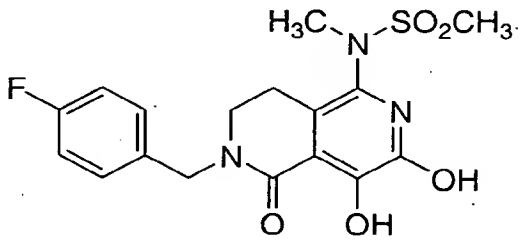
To methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (0.178 g, 0.514 mmol) in wet methanol was added N,N-dimethylamine in MeOH (4.0 eq.). The reaction mixture was put in a microwave reactor where it was heated at 130 °C for 1.5 hours, after which the reaction mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a solid. Alternatively, the starting material can be treated with LiOH in 1:1:1 THF/MeOH/H_2O to give the product.

^{1}HNMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.06 (m, 2H), 4.74 (s, 2H), 3.48 (m, 2H), 3.32 (m, 2H).

ES MS M+1 = 333

EXAMPLE 8

N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide



Step 1: 1-(glycyloxy)butane chloride

To a suspension of glycine hydrochloride (10g, 89.6 mmol) in 250 mL butanol under nitrogen was added thionyl chloride (45.7 mL, 627 mmol) dropwise. After the addition was complete, the solution was heated at 70 °C overnight. The volatile components were removed on the roto-evaporator and the residue was suspended and evaporated from toluene three times. The resulting crude gum was dissolved in an equal weight of toluene for easy transfer and was used as is in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (bs, 3H), 4.18 (t, *J*=6.7 Hz, 2H), 4.0 (bs, 2H), 1.62 (m, 2H), 1.38 (m, 2H), 0.92 (t, *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 132.

Step 2: Butyl N-[ethoxy(oxo)acetyl]glycinate

A 1:1 by weight solution of 1-(glycyloxy)butane chloride (10g, 59.6 mmol) in toluene (10g) was treated with EtOH ((100 mL), then Triethylamine (10 mL, 71.6 mmol) and diethyloxalate (16.2 mL, 119.3 mmol) and heated to 50 °C for three hours. . The volatile components were removed on the roto-evaporator and the residue was dissolved in $CHCl_3$, washed two times with 10% $KHSO_4$, the aqueous layer was washed two times with $CHCl_3$, the organic layers were combined, dried over Na_2SO_4, filtered and evaporated to give the crude oil, which was chromatographed on silica eluting first with 20% EtOAc/hexanes and then with 50% EtOAc/hexanes to give clean product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 4.37 (q, *J*=7.2 Hz, 2H), 4.2 (t, , *J*=6.6 Hz, 2H), 4.12 (d, *J*=5.5 Hz, 2H), 1.64 (p, *J*=6.8 Hz, 2H), 1.39 (t, *J*=7.15 Hz, 3H), 1.37 (m, buried, 2H), 0.94 (t, , *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 232

Step 3: Ethyl 5-butoxy-1,3-oxazole-2-carboxylate

A suspension of P_2O_5 (22g, 155.6 mmol) in CH_3CN (50 mL) under nitrogen was warmed to 50 °C and treated with butyl N-[ethoxy(oxo)acetyl]glycinate (6g, 25.9 mmol) dissolved in 10

mL CH_3CN. The mixture was heated to 65 °C for 1.5 hours, then cooled in an ice bath. Ice and brine were added to the reaction mixture, then EtOAc was added and the mixture transferred to a separatory funnel. $CHCl_3$ was added to dissolve solids and the organic layer was isolated. The aqueous layer was washed repeatedly with $CHCl_3$ and EtOAc, the organic layers were combined and dried with Na_2SO_4, then concentrated. The residue was chromatographed on silica eluting with a gradient of 0-30% EtOAc/Hexanes to give the product as a clear, colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.42 (q, *J*=7.15 Hz, 2H), 4.18 (t, *J*=6.4 Hz, 2H), 1.8 (p, *J*=6.4 Hz, 2H), 1.47 (p, *J*=7.4 Hz, 2H), 1.41 (t, *J*=7.15 Hz, 3H), 0.97 (t, *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 214.

Step 4: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

In a heavy walled round bottom flask with screw top were combined ethyl 5-butoxy-1,3-oxazole-2-carboxylate (2.53g, 11.88mmol) and 1-(4-fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one (1.22g, 5.94 mmol; see Example 1, Step 3) and trifluoroacetic acid (0.46 mL, 5.94 mmol). The vessel was sealed and placed in an oil bath heated to 130 °C. The reaction mixture was stirred for 3 days. The dark brown reaction mixture was cooled and a crystalline precipitate formed. The mixture was diluted with ether and the solids collected by filtration and washed with ether to give the product as tan shiny plates. Further product can be obtained by evaporating the mother liquor, adding more trifluoroacetic acid and re-heating the mixture.

^1H NMR (400 MHz, $CDCl_3$) δ 12.9 (s, 1H), 8.42 (s, 1H), 7.31 (dd, *J*=5.3, 8.8 Hz, 2H), 7.06 (t, *J*=8.6 Hz, 2H), 4.72 (s, 2H), 4.41 (q, *J*=7.15 Hz, 2H), 3.50 (m, 4H), 1.41 (t, *J*=7.15 Hz, 3H) ppm. ES MS M+1 = 345.

Step 5: Ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a solution of chloroform (10 mL) and methanol (10 mL) was added trimethylsilyl diazomethane (2.0 M in hexanes, 5 mL, 0.01 mole). After stirring for 10 minutes at room temperature, 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-2-ium trifluoracetic acid salt (1.6 g, 3.5 mmol) in chloroform was added. After 7 hours, methanol (5 mL) and trimethylsilyl diazomethane (2.5 mL, 0.005 mole) was added to the reaction mixture. After 1 hour, glacial acetic acid (3 mL) was added with gas evolution observed. The solution was stirred for 0.5 hour. The product mixture was concentrated under vacuum. The residual material was subjected to column

chromatography on silica gel eluting with 0-100 % ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to afford the title compound as a foam.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.32 (dd, *J*=5.3, 8.5 Hz, 2H), 7.03 (t, *J*=8.6 Hz, 2H), 4.73 (s, 2H), 4.45 (q, *J*=7.14 Hz, 2H), 4.11 (s, 3H), 3.43 (t, *J*=6 Hz, 2H), 3.29 (t, *J*=6 Hz, 2H), 1.42 (t, *J*=7.2 Hz, 3H) ppm. ES MS M+1 = 359

Step 6: 6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (1.21 g, 3.38 mmol) in methanol (5 mL) and water (5 mL) and THF (5 mL) was added lithium hydroxide (0.425 g, 10.13 mmol). After 5 minutes, 1N HCl (3 equiv.) was added to the product mixture, which was then dried under vacuum to provide the crude title compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (br, 1H), 8.35 (s, 1H), 7.27 (m, 2H), 7.03 (m, 2H), 4.73 (s, 2H), 4.15 (s, 3H), 3.55 (m, 4H) ppm. ES MS M+1 = 331

Step 7: 6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl chloride

A solution of 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carboxylic acid (1.11 g, 3.36 mmol) in thionyl chloride (0.4 g, 3.36 mmol) was heated to 110 °C. After 0.5 hours, the product mixture was concentrated under vacuum. The residue was suspended in toluene, evaporated, then suspended in chloroform and evaporated to give the title compound. The product was assayed by quenching in methanol solution to produce the methyl ester. ES MS M+1 = 345 (methyl ester forms after quench in methanol)

Step 8: 5-Amino-2-(4-fluorobenzyl)-8-methoxy-3,4-dihydro-2,6-naphthyridin-1(2H)-one

To a solution of sodium azide (0.24 g, 3.69 mmol) in water (2.5 mL) was added 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl chloride (1.17 g, 3.36 mmol) in acetone (15 mL). After 20 minutes, the product mixture was concentrated under vacuum to provide 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl azide. The crude azide (1.19 g, 3.35 mmol) in DMF (20 mL) was heated to 110 °C. After 20 minutes, the product mixture was cooled for 10 minutes, then 1N NaOH (3.3 mL) was added. After 20 minutes, the mixture was concentrated under vacuum, re-dissolved in toluene and $CHCl_3$ and evaporated. The residue was partitioned between $CHCl_3$ and saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.32 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.71 (s, 2H), 4.17 (s, 2H), 3.94 (s, 3H), 3.47 (t, *J*=6 Hz, 2H), 2.58 (t, *J*=6 Hz, 2H) ppm. ES MS (m+1) = 302.

Step 9: *N*-[6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]methanesulfonamide

To a solution of 5-amino-2-(4-fluorobenzyl)-8-methoxy-3,4-dihydro-2,6-naphthyridin-1(2H)-one (0.889 g, 2.95 mmol) in pyridine (5 mL) was added dropwise methanesulfonyl chloride (0.575 g, 5.016 mmol). After stirring for an hour at room temperature, the product mixture was quenched with pH 7 buffer, then concentrated under vacuum. The residue was dissolved in $CHCl_3$ and pH 7 buffer, the pH of the aqueous layer was adjusted to pH 5 with 1N NaOH and the layers separated. Several more extractions with $CHCl_3$ were performed. The organic extracts were dried with Na_2SO_4, filtered, and concentrated under vacuum, then dissolved in toluene and $CHCl_3$ and evaporated to provide the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.70 (s, 2H), 4.03 (s, 3H), 3.44 (t, *J*=6.5 Hz, 2H), 3.21 (s, 3H), 2.89 (t, *J*=6.4 Hz, 2H) ppm. ES MS (m+1) = 380.

Step 10: *N*-[6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]methanesulfonamide (0.097 g, 0.256 mmol) in DMF (2 mL) was added Cs_2CO_3 (0.083 g, 0.256 mmol) and MeI (0.04 g, 0.28 mmol, dissolved in DMF). After stirring for 2 hours, additional MeI (0.02 g, 0.14 mmol) was added. The product mixture was concentrated. The residue was partitioned between $CHCl_3$ and pH 7 buffer. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.26 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.70 (s, 2H), 4.06 (s, 3H), 3.43 (t, *J*=7 Hz, 2H), 3.21 (s, 3H), 3.03 (m, 5H) ppm. ES MS (m+1) = 394.

Step 11: *N*-[6-(4-Fluorobenzyl)-4-methoxy-2-oxido-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.35 g, 0.89 mmol) in CH_2Cl_2 (10 mL) was added mCPBA (1.08 g, 6.23 mmol) in portions. After stirring for 3.5 hours at reflux, the product mixture was cooled to room temperature, 1 mL of ethanol was added, and the solution was concentrated. The residue was partitioned between $CHCl_3$ and saturated Na_2SO_3. The organic layer was extracted repeatedly with

saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the crude title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.30(m, 2H), 7.03 (t, *J*=7 Hz, 2H), 4.72 (d, *J*= 14.6 Hz, 1H), 4.65 (d, J = 14.6 Hz, 1H), 4.01 (s, 3H), 3.45 (m, 2H), 3.29 (s, 3H), 3.20 (s, 3H), 3.18 (m, 1H), 2.87 (m, 1H) ppm. ES MS (m+1) = 410.

Step 12: *N*-[6-(4-Fluorobenzyl)-3-hydroxy-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

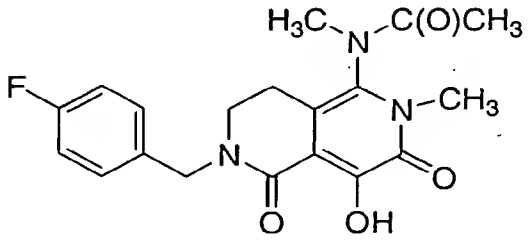
A solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-2-oxido-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.36 g, 0.889 mmol) in acetic anhydride (10 mL) was heated to 110 °C for 3 hours, then evaporated to dryness to give the intermediate 6-(4-fluorobenzyl)-4-methoxy-1-[methyl(methylsulfonyl)amino]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl acetate (ES MS (m+1) = 452). The crude material was dissolved in methanol (6 mL) and treated with sodium methoxide (30 % by weight in methanol, 0.5 mL, 2.6 mmol). After 1 hour, the product mixture was neutralized with 6 N HCl, then concentrated. The residue was partitioned between $CHCl_3$ and 10% $KHSO_4$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.71 (bs, 2H), 4.06 (s, 3H), 3.41 (t, *J*=6 Hz, 2H), 3.28 (s, 3H), 3.11 (s, 3H), 2.8 (m, 2H) ppm. ES MS (m+1) = 410.

Step 13: N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5;6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-3-hydroxy-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.0207 g, 0.506 mmol) in CH_2Cl_2 (6 mL) was added 30% by weight HBr in propionic acid (0.196 g HBr, 2.42 mmol). Alternatively, 30% HBr in acetic acid can be used. After 1.5 hours, the product mixture was evaporated and the residue partitioned between $CHCl_3$ and 10% $KHSO_4$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 12.97 (br, 1H), 7.28 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.69 (s, 2H), 3.46 (t, *J*=7 Hz, 2H), 3.24 (s, 3H), 3.09 (s, 3H), 2.98 (m, 2H) ppm. ES MS (m+1) = 396.

EXAMPLE 9

N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

To 5-(ethoxycarbonyl)-2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydro-2,6-naphthyridin-6-ium trifluoroacetate (0.5 gm, 1.09 mmol; see Example 8, Step 4) in glacial acetic acid (25 mL) at room temperature under nitrogen was added, with stirring, aqueous peroxide (30% by wt) (1.24 mL, 10.9 mmol). The reaction was warmed to 100 °C and stirred for 1.5 hours. The reaction was allowed to cool, ethanol (1 mL) was added and volatile components were removed under reduced pressure. The resulting oil was placed under high vacuum for 16 hours, then used as is. Alternatively, after cooling, water can be added and the volatile components removed under reduced pressure. The residue can be partitioned between $CHCl_3$ and saturated Na_2SO_3. The organic extract can be dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 12.8 (br, 1H), 7.90 (s, 1H), 7.28 (dd, J = 5.3, 8.5 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 4.69 (s, 2H), 4.43 (q, J = 7.14 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.37 (t, J = 7.14 Hz, 3H) ppm. ES MS (m+1) = 361.

Step 2: Sodium 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-4-olate

To ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (2.3 gm, 6.38 mmol) in neat acetic anhydride (24 mL) was stirred under nitrogen at 100 °C for 1 hour. The reaction was concentrated to an oil under reduced pressure and dry methanol (20 mL) was added followed by a methanolic sodium methoxide solution (30% by wt) (4.54 mL, 25.2 mmol). The reaction was stirred at room temperature for 1 hour. The reaction was then concentrated to an oil under reduced pressure and crystallized from a small amount of methanol (~5 mL). The crystals were collected by filtration, washed an additional 10 mL of methanol and dried in vacuo to give the desired product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (br, 1H), 7.30 (m, 2H), 7.06 (t, *J*=9 Hz, 2H), 4.71 (s, 2H), 4.36 (q, *J*=7 Hz, 2H), 3.44 (t, *J*=6 Hz, 2H), 3.33 (t, *J*=6 Hz, 2H), 1.38 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 361.

Step 3: Ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of sodium 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-4-olate (1.45 g, 3.79 mmol) in DMF (20 mL) was added cesium carbonate (4.94 g, 15.1 mmol). After 5 minutes, methyl iodide (2.15 g, 15.1 mmol) was added. The reaction mixture was stirred at room temperature. After 24 hours, the product mixture was concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-3 % methanol in CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the *N*- and *O*-methylated compounds separately.

N-methylated compound: Ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.02 (t, *J*=9 Hz, 2H), 4.69 (s, 2H), 4.39 (q, *J*=7 Hz, 2H), 4.13 (s, 3H), 3.51 (s, 3H), 3.53 (t, *J*=6 Hz, 2H), 2.59 (t, *J*=6 Hz, 2H), 1.38 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 389.

O-methylated compound: Ethyl 6-(4-fluorobenzyl)-3,4-dimethoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.73 (s, 2H), 4.37 (q, *J*=7 Hz, 2H), 4.05 (m, 6H), 3.38 (t, *J*=6 Hz, 2H), 3.14 (t, *J*=6 Hz, 2H), 1.39 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 389.

Step 4: 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (1.15 g, 2.96 mmol) in 1:1:1 MeOH/H_2O/THF (15 mL) was added LiOH (0.37g, 8.88 mmol) and the solution was stirred for 2 hours. A solution of 1 N HCl (8.9 mL) was added, the solution was concentrated and $CHCl_3$ and 10% $KHSO_4$ were added. The layers were separated and the aqueous was extracted repeatedly. The combined organic layers were filtered and the solid collected. The remaining organic was dried over Na_2SO_4, filtered, combined with the collected solid and evaporated to give the crude product.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (dd, *J*=5.6, 8.6 Hz, 2H), 7.16 (t, *J*=8.8 Hz, 2H), 4.64 (s, 2H), 3.84 (s, 3H), 3.42 (s, 3H), 3.4 (t, *J*=6 Hz, 2H), 2.6 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 361.

Step 5: 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carbonyl chloride

To 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (0.213g, 0.6 mmol) was added thionyl chloride (5 mL) and the mixture was heated to reflux for 2 hours, then evaporated to dryness, suspended in toluene and evaporated three times to give the crude product.

^{1}H NMR (400 MHz, CDCl^3) δ 7.30 (dd, *J*=5.3, 8.6 Hz, 2H), 7.03 (t, *J*=8.8 Hz, 2H), 4.7 (s, 2H), 4.18 (s, 3H), 3.58 (s, 3H), 3.39 (t, *J*=6 Hz, 2H), 2.65 (t, *J*=6 Hz, 2H)ppm.
ES MS M+1 = 379.

Step 6: 5-amino-2-(4-fluorobenzyl)-8-methoxy-6-methyl-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione

To a solution of sodium azide (0.091g, 1.4 mmol) in 2 mL water cooled to 0 °C was add 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carbonyl chloride (0.48g, 1.28 mmol) in acetone (8 mL). The solution was stirred for 30 minutes, then evaporated. The residue was partitioned between $CHCl_3$ and saturated Na bicarbonate, dried with Na_2SO_4, filtered and evaporated to give the crude product, which was chromatographed on silica eluting with 5% MeOH/$CHCl_3$ saturated with NH_3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J*=5.5, 8.4 Hz, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.7 (s, 2H), 4.05 (bs, 2H), 3.96 (s, 3H), 3.56 (s, 3H), 3.37 (t, *J*=6 Hz, 2H), 2.42 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 332.

Step 7: N-acetyl-N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide

To 5-amino-2-(4-fluorobenzyl)-8-methoxy-6-methyl-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione (0.119mg, 0.36 mmol) in a sealable microwave tube was added acetic anhydride (3.5 mL) and the solution was heated to 150 °C for 25 minutes in a microwave. The solution was evaporated to dryness to give the crude product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.02 (t, *J*=8.6 Hz, 2H), 4.69 (s, 2H), 4.14 (s, 3H), 3.37 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 2.37 (t, *J*=6 Hz, 2H), 2.32 (s, 6H)ppm.
ES MS M+1 = 416.

Step 8: N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide

To N-acetyl-N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide (0.149g, 0.36 mmol) in MeOH (5 mL) cooled to 0 °C was added 30% weight solution NaOMe in MeOH (0.2 mL, 1.07 mmol). The reaction was warmed to room temperature for 40 minutes, then 1 N HCl was added (1.07 mL) and the reaction was concentrated, and $CHCl_3$ and 10% $KHSO_4$ were added. The layers were separated and the aqueous was extracted repeatedly. The organic layer was dried over Na_2SO_4, filtered, combined with the collected solid and evaporated to give the crude product.

^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.26 (m, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.65 (bs, 2H), 3.96 (s, 3H), 3.39 (s, 3H), 3.33 (t, *J*=6 Hz, 2H), 2.45 (bs, 2H), 2.23 (s, 3H)ppm. ES MS M+1 = 374.

Step 9: N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide

To N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide (0.073g, 0.196 mmol) in 2 mL DMF was added Cs_2CO_3 (0.084g, 0.25 mmol) and methyl iodide (0.044 mL, 0.7 mmole) and the reaction was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between $CHCl_3$ and 10% $KHSO_4$, the organic was dried with Na_2SO_4, filtered and evaporated to give the crude product.

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.4, 8.5 Hz, 2H), 7.03 (t, , *J*=8.6 Hz, 2H), 4.70 (s, 2H), 4.14 (s, 3H), 3.43 (s, 3H), 3.37 (m, 2H), 3.08 (s, 3H), 2.48 (m, 2H), 1.87 (s, 3H) ppm. ES MS M+1 = 388.

Step 10: N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide

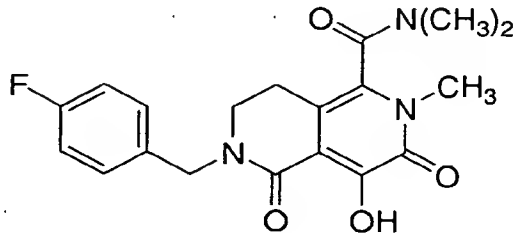
To N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide (0.070g, 0.181 mmol) was dissolved in 1 mL glacial acetic acid and 0.75 mL 30% by weight HBr in acetic acid solution was added. The reaction was stirred for 1.5 hours, water was added and the reaction evaporated to dryness under vacuum. The residue was purified on reverse phase and the fractions collected and evaporated. The residue was dissolved in dioxane, from which crystals formed and were collected. The crystals were dried under vacuum with heat to give the product.

^1H NMR (400 MHz, $CDCl_3$) δ 13.17 (s, 1H), 7.30 (dd, *J*=5.3, 8.7 Hz, 2H), 7.03 (t, , *J*=8.7 Hz, 2H), 4.73 (d, *J*=14.6 Hz, 1H), 4.66 (d, *J*=14.6 Hz, 1H), 3.44 (s, 3H), 3.41 (m, 2H), 3.08 (s, 3H), 2.61 (m, 2H), 1.86 (s, 3H) ppm.

ES MS M+1 = 374.

EXAMPLE 10

6-(4-Fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: Methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.28 g, 0.81 mmol) in DMF (3.0 mL) was added Cs_2CO_3 (0.81 g, 2.47 mmol) at room temperature. After 10 minutes, CH_3I (0.597 g, 4.21 mmol) was added and the warmed to 40 °C. After 2.5 hours, the product mixture was partitioned between EtOAc and 1 N HCl. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-3 % methanol in CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the title compound. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2h), 7.02 (t, *J*=9 Hz, 2H), 4.68 (s, 2H), 4.12 (s, 3H), 3.91 (s, 3H), 3.48 (s, 3H), 3.32 (t, *J*=6 Hz, 2H), 2.56 (t, *J*=6.5 Hz, 2H) ppm. ES MS M+1 = 375.

Step 2: 6-(4-Fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.575 g, 1.536 mmol) in methanol was added LiOH (0.11 g, 4.61 mmol) in water. The reaction mixture was heated to reflux. After 0.5 hours, the product mixture cooled to room temperature and concentrated under vacuum. The residual material was partitioned between EtOAc and 1 N HCl. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2h), 7.03 (t, *J*=9 Hz, 2H), 4.66 (s, 2H), 3.95 (s, 3H), 3.49 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 2.68 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 361.

Step 3: 6-(4-Fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

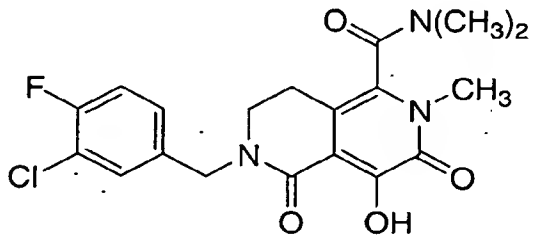
To a solution of 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (0.14 g, 0.40 mol) in DMF was added BOP (0.515 g, 1.167 mmol) and the dimethylamine (2.0 M in THF) (0.035 g, 0.778 mmol). After 24 hours, the product mixture was concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5-95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to give 6-(4-fluorobenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (ES MS M+1= 388) . A solution of this product (0.1 g, 0.3 mmol) in CH_2Cl_2 was treated with HBr (30 wt % in acetic acid) (0.104 g, 1.29 mmol) and after stirring at room temperature for 24 hours, concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound.

^{1}HNMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.56 (d, *J* = 14.8 Hz, 1H), 3.49 (t, *J*=6 Hz, 2H), 3.43 (s, 3H), 3.08 (s, 3H), 2.93 (s, 3H), 2.59 (t, *J*=6 Hz, 2H) ppm.

ES MS M+1 = 374.

EXAMPLE 11

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

In a manner similar to that described for 6-(4-fluorobenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (Example 10, Step 3), 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide was prepared starting from p-methoxybenzyl chloride, and the material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA).

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.82 (d, *J*=14.5 Hz, 1H), 4.46 (d, *J*=14.5 Hz, 1H), 4.07 (s, 3H), 3.78 (s, 3H), 3.45 (s, 3H), 3.40 (m, 1H), 3.30 (m, 1H), 3.09 (s, 3H), 2.90 (s, 3H), 2.51 (m, 1H), 2.35 (m, 1H) ppm. (ES MS M+1= 400.1)

Step 2: 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

A solution of 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.18g, 0.45 mmol) in toluene (about 3 mL) was treated with p-toluene sulfonic acid (0.34g, 1.8 mmol). The mixture was heated to 110 °C for 4 hours, then cooled and concentrated under vacuum. The residue was partitioned between water and EtOAc, the aqueous layer concentrated,and the residue purified by reverse phase chromatography to give the title product.

^{1}HNMR (400 MHz, CD_3OD) δ 3.44 (m, 5H), 3.10 (s, 3H), 2.97 (s, 3H), 2.60 (t, *J*= 6.6 Hz, 2H) ppm. (ES MS M+1= 266.2)

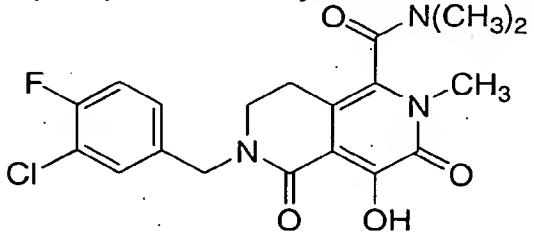
Step 3: 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

A solution of 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.018g, 0.068 mmol) in DMF (2 mL) was treated with Cs_2CO_3 (0.066g, 0.2 mmol) and 3-chloro-4-fluoro benzyl bromide (0.045g, 0.2 mmol) and heated to 40 °C. The reaction mixture was then cooled to 0 degrees C, a suspension of NaH (95% dispersion in oil, 0.2 mmol) was added and the reaction was warmed to room temperature. After 1 hr the reaction was partitioned between ice water and EtOAc, the organic layer was dried with brine and Na_2SO_4, filtered and evaporated to give 6-(3-chloro-4-fluorobenzyl)-4-[(3-chloro-4-fluorobenzyl)oxy]-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (ES MS M+1= 549.9) . This material was then dissolved in CH_2Cl_2 (3 mL) and treated with 4 drops of a 30% by weight solution of HBr in propionic acid at room temperature. After 20 minutes the solution was concentrated and purified by reverse phase chromatography to give the product.

^{1}HNMR (400 MHz, CD_3OD) δ 7.48 (m, 1H), 7.32 (m, 1H), 7.22 (t, *J*=8.5 Hz, 1H), 4.76 (d, *J*=14.8 Hz, 1H), 4.63 (d, *J*=14.8 Hz, 1H), 3.50 (t, *J*=6.4 Hz, 2H), 3.44 (s, 3H), 3.08 (s, 3H), 2.95 (s, 3H), 2.61 (t, *J*=6.2 Hz, 2H) ppm. (ES MS M+1= 407.9)

EXAMPLE 12

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 1-(3-Chloro-4-fluorobenzyl)piperidin-2-one

Valerolactam (153.3 g, 1.54 mol) was dissolved in NMP (3.5 L) and cooled to 0 °C. NaH (67.7g, 1.69 mol, 60% dispersion in oil) was added in portions over 5 min keeping the temperature at 0 °C. The reaction was stirred for 30 min, and 3-chloro-4-fluorobenzylbromide (345.5 g, 1.54 mol) dissolved in 200 mL NMP was added over 30 min, again keeping the internal temperature at 0 °C. The reaction was aged for 1 hour at 0 °C, and allowed to warm to room temperature overnight. LCMS showed the reaction complete. The reaction mixture was quenched with 5L distilled H_2O, extracted with 3 portions of CH_2Cl_2 (2L, 1L, 1L) and the organic layers combined and washed with three 4L portions of water. The organic layer was concentrated and was found to contain NMP. The residual oil was dissolved in EtOAc (4 L), and extracted with three 2L portions of water. The organic layer was concentrated to give the product that solidified upon standing.

^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.0 (m, 2H), 7.1 (m, 1H), 4.56 (s, 2H), 3.19 (t, J = 4.9, 2H), 2.46 (t, J = 6.4, 2H), 1.8-1.75 (m, 4H) ppm.

Step 2: 1-(3-Chloro-4-fluorobenzyl)-5,6-dihydropyridin-2(1H)-one

1-(3-Chloro-4-fluorobenzyl)piperidin-2-one (340g, 1.41 mol) was dissolved in THF (5 L) and cooled to -20 °C under nitrogen. LHMDS (3.09L, 3.09 mol, 1M in THF) was added over 40 min keeping the temperature at -20 °C and aged for 1 hr at -20 °C. The methyl benzene sulfonate (231 mL, 1.69 mol) was added over 30 min, again keeping the internal temperature at -20 °C. The reaction was aged for 30 min at -20 °C and LCMS showed the reaction complete. The reaction mixture was diluted with 4L EtOAc and washed with four 2L portions of distilled H_2O. The organic layer was concentrated and the residue was dissolved in 4L toluene. Na_2CO_3 (500g) was added and the reaction heated to 100 °C for 1 hour. LCMS showed the reaction complete. The residue was diluted with 4 L EtOAc and washed with four 2L portions of distilled water. The organic layer was concentrated and the residue purified by flash chromatography on silica eluting with a gradient of 0-60% EtOAc/heptane. The product was isolated as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 1H), 7.15 (m, 1H), 7.1 (t, 1H), 6.6 (m, 1H), 6.0 (m, 1H), 4.55 (s, 2H), 3.33 (t, 2H), 1.38 (m, 2H) ppm. (ES MS M+1 = 240.13)

Step 3: 2-Butoxy-2-oxoethanaminium chloride

Glycine hydrochloride (400g, 3.58 mol) was suspended in 8 L of n-butanol and thionyl chloride (1.37L, 18.84 mol) was added slowly dropwise (exotherm). After addition was complete, the reaction was heated to 70 °C overnight. The reaction could be followed by spotting directly on TLC, pumping off the volatiles, eluting with 10% MeOH/$CHCl_3$ saturated with NH_3, and staining in ninhydrin. The next day the reaction was stripped to dryness under vacuum and the residue was triturated with heptane/EtOAc to give the product as a white solid after drying on a filter under Nitrogen.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (bs, 3H), 4.18 (t, J = 6.7 Hz, 2H), 4.0 (bs, 2H), 1.62 (m, 2H), 1.38 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H) ppm. ES MS M+1 = 132.

Step 4: Butyl N-[ethoxy(oxo)acetyl]glycinate

2-Butoxy-2-oxoethanaminium chloride (573.5g, 3.42 mol) was suspended in 7 L of ethanol and triethylamine (415g, 4.1 mol) was added. Diethyloxalate (1.0Kg, 6.8 mol) was added and the reaction warmed to 50 °C for 3 hours. The reaction was cooled, the volatiles were removed under vacuum and the residue was dissolved in methylene chloride and washed with two 4L portions of water and dried over $MgSO_4$. The next day the reaction was filtered, evaporated to give ~1.2 Kg of an oil that was chromatographed on silica eluting with Heptane/EtOAc to give product.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.2 (t, J = 6.6 Hz, 2H), 4.12 (d, J = 5.5 Hz, 2H), 1.64 (p, J = 6.8 Hz, 2H), 1.39 (t, J = 7.15 Hz, 3H), 1.37 (m, buried, 2H), 0.94 (t, J = 7.4 Hz, 3H) ppm. ES MS M+1 = 232.

Step 5: Ethyl 5-butoxy-1,3-oxazole-2-carboxylate

Butyl N-[ethoxy(oxo)acetyl]glycinate (783g, 3.38 mol) was dissolved in 8 L of acetonitrile in a 50L Chemglass reactor with overhead stirrer and P_2O_5 (415g, 2.92 mol) was added in large portions, watching for exotherm. The reaction was heated to 60 °C for 1 hour and LCMS showed the reaction done. After cooling, water (8L) was added at 20 °C and the reaction was transferred to a 50L flask. Methylene chloride (8L) was added, the layers split and the aqueous layer was extracted with three 2L volumes of methylene chloride. The combined organic layers were washed with two 4L portions of saturated aqueous $NaHCO_3$, then dried with $MgSO_4$ and evaporated to give an oil that was purified on silica eluting with 0-30% EtOAc/heptane to give the product as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.42 (q, J = 7.15 Hz, 2H), 4.18 (t, J = 6.4 Hz, 2H), 1.8 (p, J = 6.4 Hz, 2H), 1.47 (p, J = 7.4 Hz, 2H), 1.41 (t, J = 7.15 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H) ppm. ES MS M+1 = 214.

Step 6: Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 5-butoxy-1,3-oxazole-2-carboxylate (44.5g, 208.6 mmol) and 1-(3-chloro-4-fluorobenzyl)-5,6-dihydropyridin-2(1H)-one (25g, 104.3 mmol) were placed in a heavy walled round bottom flask equipped with a screw top and acid resistant O-ring and a stir bar. The mixture was stirred and water (2.82 mL, 156.7 mmol) was added. The reaction was sealed and placed in an oil bath pre-heated to 130 °C. The reaction was aged for 72 hours, when LCMS showed much of the lactam had been consumed. The reaction was allowed to cool and sit until the mass had solidified. The mass was taken up in ether and the solids collected by filtration to give the product as a tan solid. The product was further purified by crystallization from EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.42 (s, 1H), 7.4 (dd, J = 2, 7Hz, 1H), 7.2 (m, 1H), 7.15 (t, J = 8.6 Hz, 1H), 4.7 (s, 2H), 4.4 (q, J = 7 Hz, 2H), 3.5 (m, 4H), 1.4 (t, J = 7 Hz, 3H) ppm. (ES MS M+1 = 379.0)

Step 7: Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (22g, 58 mmol) was dissolved in 500 mL glacial acetic acid and H_2O_2 (30% by weight in water, 65.8 mL) was added. The reaction was warmed to 100 °C and aged for four hours at which time LCMS showed the reaction done. The solution was cooled in an ice bath to 25 °C and treated with saturated Na_2SO_3 solution, keeping the temperature below 40 °C. When starch paper test showed no peroxides present, the solution was concentrated by 1/3, the pH was adjusted to ~3 with aqueous HCl and the solution extracted with CH_2Cl_2 several times. The organic layers were dried over Na_2SO_4, filtered and evaporated to give product as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 7.9 (s, 1H), 7.38 (dd, J = 2, 7Hz, 1H), 7.27-7.1 (m, 2H), 4.66 (s, 2H), 4.44 (q, J = 7 Hz, 2H), 3.52 (t, J = 7Hz, 2H), 2.90 (t, J = 7Hz, 2H), 1.38 (t, J = 7 Hz, 3H) ppm. (ES MS M+1 = 395.0)

Step 8: Ethyl 3,4-bis(acetyloxy)-6-(3-chloro-4-fluorobenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (23g, 58 mmol) was dissolved in 400 mL acetic anhydride and heated with stirring under nitrogen to 100 °C for 1 hour. By LCMS, the starting material and product are very close in retention time. To check that the reaction was done, an aliquot was treated with NaOMe in water and CH_3CN. The resulting hydrolyzed product elutes at an earlier retention time and allows distinguishing between remaining N-oxide and rearranged product. The reaction was evaporated to give the crude product as an oily residue that was taken on to the next step.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 1H), 7.2-7.1 (m, 1H), 7.12 (t, J = 8Hz, 1H), 4.68 (bs, 2H), 4.4 (q, J = 7 Hz, 2H), 3.48 (m, 2H), 3.35 (m, 2H), 2.38 (bs, 6H), 1.4 (t, J = 7 Hz, 3H) ppm. (ES MS M+1 = 394.9)

Step 9: Methyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 3,4-bis(acetyloxy)-6-(3-chloro-4-fluorobenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (27.8g, 58 mmol) was dissolved in 300 mL MeOH and treated with a 30% by weight solution of NaOMe in MeOH (41.8 mL, 232 mmol, 4 equivalents was sufficient to get the pH of the reaction to 9) for 5 hours at 40 °C. LCMS showed the cleavage of the acetate groups was complete, a little transesterification was observed as well. The volume was reduced by half under vacuum and the mixture was diluted with THF (400 mL) and an additional 33mL of NaOMe was added. The reaction was stirred at rt overnight and then warmed to 50 °C for four hrs, when LCMS showed transesterification completed. The reaction was neutralized with 1N HCl and allowed to sit at room temperature overnight, then later acidified to pH 3 and extracted with $CHCl_3$ several times. The organic layer was dried over Na_2SO_4 and evaporated to give a black oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0-8.2 (bs, 1H), 7.38 (dd, J = 6.8. 2Hz, 1H), 7.2 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 4.68 (s, 2H), 3.92 (s, 3H), 3.46 (t, J = 6.4 Hz, 2H), 3.34 (t, J = 6.4 Hz, 2H) ppm. (ES MS M+1 = 380.9)

Step 10: Methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (18.00 g, 47 mmol) in DMF (200 mL) was added magnesium methylate (96.08 mL, 95 mmol), and the reaction was warmed for 1 hour and cooled. The reaction was treated with iodomethane (17.66 mL, 283 mmol) and stirred at 45 °C overnight. At this time, LCMS showed the reaction incomplete, and an additional equivalent of iodomethane (2.95 mL, 48 mmol) was

added. The reaction was again stirred for 4 hours. The solvent was removed *in vacuo*, and the resulting oil was partitioned between chloroform and 1N HCl. The aqueous layer was washed twice more with chloroform. The organic fractions were extracted with 10% sodium bisulfite, and the bisulfite layer was washed twice with chloroform. The combined organic layers were washed with 5% aqueous HCl and brine, dried over sodium sulfate and concentrated *in vacuo* to afford the product as a black oil. This material appears quite clean by NMR and HPLC, but is highly colored.
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 1H), 7.35 (dd, J = 2.4, 6.9 Hz, 1H), 7.22-7.18 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 4.67 (s, 2H), 3.92 (s, 3H), 3.54 (s, 3H), 3.43 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H) ppm. (ES MS M+1 = 395.0)

Step 11: Methyl 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (7.25 g, 18 mmol) in anhydrous DMF (75 mL) was added cesium carbonate (5.98 g, 18 mmol) and iodomethane (2.86 mL, 46 mmol). The reaction was stirred at room temperature overnight, and LCMS showed 70% completion. The reaction was heated to 50 °C for 7 hours and then allowed to stir at room temperature again overnight. LCMS indicated completion. The reaction was concentrated to dryness, and the resulting residue was dissolved in chloroform. The solution was extracted twice with saturated Na_2SO_3 solution, dried over sodium sulfate, filtered, and evaporated to afford a dark brown oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 2.1, 7.0 Hz, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 4.65 (s, 2H), 4.12 (s, 3H), 3.92 (s, 3H), 3.49 (s, 3H), 3.34 (m, 2H), 2.59 (m, 2H) ppm. (ES MS M+1 = 409.0)

Step 12: 6-(3-Chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of methyl 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (14.3 g, 35 mmol) in THF (150mL) and MeOH (150 mL) was added LiOH (2.74g, 114 mmol) dissolved in 114 mL water and the reaction was heated to 50 °C for 45 min. HPLC showed completion. The reaction was neutralized with 1N HCl and cooled to room temperature. THF was removed *in vacuo*, and the resulting slurry was partitioned between $CHCl_3$ and 5% aqueous HCl. The aqueous was washed with additional $CHCl_3$. The combined organics were dried over sodium sulfate, filtered, and concentrated to dryness to afford the desired product as a pale yellow foam. The material was crystallized from ethyl acetate to give a light yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (dd, J = 2.0, 6.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.25-7.20 (m, 1H), 4.71 (s, 2H), 3.98 (s, 3H), 3.58 (s, 3H), 3.50 (m, 2H), 2.77-2.74 (m, 2H) ppm. (ES MS M+1 = 395.0)

Step 13: 6-(3-Chloro-4-fluorobenzyl)-4-methoxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To a suspension of 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (8.50 g, 22 mmol) in methylene chloride (300 mL) at 0 °C was added oxalyl chloride (2.25 mL, 26 mmol) and 1 drop of anhydrous DMF. The reaction was stirred at 0 °C for 15 min during which time no bubbling was observed. The reaction was then allowed to warm to room temperature and stirred for 40 min. At this time bubbling had ceased, and all material was in solution. An aliquot of the solution was quenched with dimethylamine and checked by LCMS to confirm completion. To the solution of the acid chloride starting material at 0 °C was added dimethylamine in THF (43.56 mL, 87 mmol, 2.0 M). The green/yellow reaction was allowed to stir at room temperature overnight although the reaction appeared to proceed immediately by LCMS. The solvent was removed *in vacuo*, and the resulting residue was dissolved in chloroform. The solution was washed with water and 5% aqueous HCl solution and back extracted to recover the product. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting iridescent green/yellow residue was examined in several TLC solvent systems (95:5 CH_2Cl_2:MeOH, 2:1 acetone:hexanes, 1:1 EtOAc:hexanes) with the most efficient separation of some early running impurities achieved in the CH_2Cl_2:MeOH system. The material was purified by silica gel flash column chromatography, loaded as a solution in methylene chloride onto a 330 g RediSep column. Gradient elution consisted of 1.5 L each of neat CH_2Cl_2, 1% MeOH:CH_2Cl_2, 2% MeOH:CH_2Cl_2, 3% MeOH:CH_2Cl_2, 4% MeOH:CH_2Cl_2, and 5% MeOH:CH_2Cl_2, in sequential order. The desired material began to elute with 3% and was pushed off the column with 4% and 5%, yielding two sets of fraction. The earlier set afforded of the desired product plus a fluorescent green contaminant. The later set afforded clean material.

^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (dd, J = 2.0, 7.2 Hz, 1H), 7.34-7.31 (m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 4.77 (d, J = 15.2 Hz, 1H), 4.65 (d, J = 15.2 Hz, 1H), 3.97 (s, 3H), 3.52-3.48 (m, 2H), 3.45 (s, 3H), 3.11 (s, 3H), 2.97 (s, 3H), 2.57-2.54 (m, 2H) ppm. (ES MS M+1 = 422.0)

Step 14: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To 6-(3-chloro-4-fluorobenzyl)-4-methoxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (5.43 g, 13 mmol) was added 33% HBr in acetic acid (20

mL, 129 mmol), and the mixture was heated to 50 °C for 15 min to give a thick, pale brown/orange solution. By LCMS, the reaction was complete, and the acetic acid was removed *in vacuo*. The resulting residue was partitioned between chloroform and water, and the organic layer was then washed with aqueous sodium sulfite solution and brine. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a pale yellow foam. The foam was dissolved in hot isopropanol and crystallized quickly, and the crystals were collected by filtration. The material was then taken up in hot acetone which did not afford a complete solution, so the mixture was hot filtered. The resulting filtrate was allowed to cool causing crystals to form. The insoluble material from the hot acetone filtration was dissolved in hot ethanol and re-filtered. This resulting filtrate also produced large, slowly grown crystals over the course of one day. The crystals compound free base from both filtrates were collected, combined, dried for 4 hours, milled, and re-dried overnight without heat to give product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (dd, J = 2.1, 7.2 Hz, 1H), 7.36-7.33 (m, 1H), 7.23 (t, J = 8.9 Hz, 1H), 4.79 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.52 (t, J = 6.8 Hz, 2H), 3.46 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.64 (t, J = 6.8 Hz, 2H) ppm. (ES MS exact mass = 408.1113)

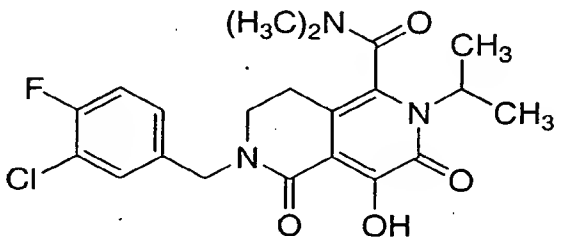
Step 15: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide sodium salt

To 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (1.08g, 2.65 mmol) in a freeze drying flask was added acetonitrile (5 mL) at room temperature. The flask was placed in an ultrasonic bath at room temp for 1 minute. Some crystals remained. Water was added (5 mL) followed by the 1 N NaOH (2.65 mL, 2.65 mmol). The total was placed in the ultrasonic bath for 1 minute. An additional 1 mL of acetonitrile was added and placed in the ultrasonic bath for an additional minute. All material was now dissolved. More water (30 mL) was added to the flask and all stayed soluble. The contents of the flask were frozen with spinning in a -78 °C acetone /dry ice bath and placed on the freeze drier for 40 hrs to give the product as a dry fluffy solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (dd, J = 2.2, 7.14 Hz, 1H), 7.33-7.29 (m, 1H), 7.17 (t, J = 9.0 Hz, 1H), 4.72 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.35 (s, 3H), 3.33-3.96 (m, 2H), 3.07 (s, 3H), 2.97 (s, 3H), 2.47 (dd, J = 5.68,11.36 Hz, 2H) ppm. (ES MS M+1 = 408.0)

EXAMPLE 13

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (27.0 g, 71 mmol) in THF (333mL) and MeOH (166 mL) was added LiOH (5.21g, 214 mmol) dissolved in enough water to make a 1N solution (total volume 213 mL) and the reaction was heated to 60 °C overnight. HPLC showed completion. A white precipitate was observed. The reaction was neutralized with 1N HCl and the more volatile solvents removed, leaving the water solution. 300 mL water was added the solution was acidified to pH 1 with 1 N HCl. A large amount of solids had precipitated. The resulting slurry was stirred vigorously with 100 mL $CHCl_3$. Most of the solid had precipitated from the partitioning and the entire mix was filtered and dried over the weekend to give product. Additional less pure product was recovered from extraction of the filtrate.
^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 7.53(dd, J = 2.2, 6.9 Hz, 1H), 7.36 (m, 1H), 7.23 (t, J = 8.9 Hz, 1H), 4.74 (s, 2H), 3.61(bt, J = 6.4 Hz, 1H), 3.50(bt, J = 6.4 Hz, 1H) ppm. (ES MS M+1 = 351.0)

Step 2: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

To a suspension of 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid (25.0 g, 71.3 mmol) in methylene chloride (1000 mL) at 0 °C was added oxalyl chloride (12.4 mL, 143 mmol) and 8 drops of anhydrous DMF. The reaction was stirred at 0 °C for 15 min. during which time no bubbling was observed. The reaction was then allowed to warm to room temperature and stirred for 40 min. At this time bubbling had ceased. An aliquot of the solution was quenched with dimethylamine and checked by LCMS. The reaction was incomplete. An additional 0.5 equivalent of oxalyl chloride was added and the reaction stirred an additional 40 min. The reaction never attained complete solution but was complete by LCMS. To the suspension of the acid chloride cooled to 0 °C was slowly added 2M dimethylamine in THF (140.8 mL, 281 mmol). The rate of addition

was adjusted to avoid a large exotherm. The pH of the solution was found to be about 9. The yellow reaction was allowed to stir at room temperature overnight although the reaction appeared to proceed immediately by LCMS. The solvent was removed *in vacuo*, and the resulting residue was dissolved in chloroform. The solution was washed with water and 5% aqueous HCl solution and the aqueous layer back extracted to recover the product. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a brown/yellow waxy solid. The initial NMR shows an excessive number of methyl group peaks, perhaps as a result of oxalyl chloride reacting with dimethylamine. A small sample was purified by reverse phase chromatography eluting with 95:5-5:95 water/acetonitrile 0.1% TFA to give clean material for NMR.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (bs, 1H), 10.9 (bs, 1H), 8.32 (s, 1H), 7.38 (dd, J = 2.0, 6.7 Hz, 1H), 7.22 (m, 1H), 7.14 (t, J = 8.5 Hz, 1H), 4.69 (s, 2H), 3.54 (t, J = 6.8 Hz, 2H), 3.14 (s, 3H), 3.05 (t, J = 6.8 Hz, 2H), 2.95 (s, 3H) ppm. (ES MS M+1 = 378.1)

Step 3: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide 2-oxide

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (24g, 63.5 mmol) was dissolved in 1000 mL glacial acetic acid and per-acetic acid (32% by weight in acetic acid, 151 mL, 635 mmol) and sodium acetate (2.6g, 31.7 mmol) was added. The reaction was warmed to 50 °C and aged overnight at which time LCMS showed the reaction done. The solution reduced in volume to 1/3 on the rotoevaporator, cooled in an ice bath and quenched slowly with 10% Na_2SO_3 solution until no peroxide was detected by a starch paper test. The reaction was transferred to a separatory funnel and water (500mL) and chloroform was added. The layers were separated and the water extracted with $CHCl_3$ several times. The combined organic layers were washed with slightly acidic water, brine and dried over Na_2SO_4, filtered and evaporated to give the product as an oil. The initial NMR shows an excessive number of methyl group peaks, perhaps as a result of oxalyl chloride reacting with dimethylamine in the second step and this impurity being carried through. A small sample was purified by reverse phase chromatography eluting with 95:5-5:95 water/acetonitrile 0.1% TFA to give clean material for NMR.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (bs, 1H), 8.4 (bs, 2H), 8.1 (s, 1 H), 7.37 (dd, J = 1.9, 6.9 Hz, 1H), 7.20 (m, 1H), 7.15 (t, J = 8.5 Hz, 1H), 4.84 (d, J = 14.7 Hz, 1H), 4.51 (d, J = 14.7 Hz, 1H), 3.61 (m, 1H), 3.59 (m, 1H), 3.15 (s, 3H), 3.05 (m, 1H)), 2.93 (s, 3H), 2.74 (m, 1H) ppm. (ES MS M+1 = 394.1)

Step 4: 6-(3-Chloro-4-fluorobenzyl)-1-[(dimethylamino)carbonyl]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-3,4-diyl diacetate

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide 2-oxide (25g, 63.5 mmol) was dissolved in 24 mL acetic anhydride and heated with stirring under nitrogen to 100 °C for 16 hours. By LCMS, the starting material and product are close in retention time and appear as the same molecular weight. To check that the reaction was done, an aliquot was treated with NaOMe in water and CH_3CN. The resulting hydrolyzed product elutes at an earlier retention time and allows distinguishing between remaining N-oxide and rearranged product. The reaction was evaporated and the residue was partitioned between chloroform and water and the water layer was back-extracted with more chloroform. The aqueous layer was checked by LCMS for product and no longer contained any. The organic layers were combined, dried over Na_2SO_4, filtered and evaporated to give an oil. (ES MS M+1 of NaOMe treated aliquot= 394.0)

Step 5: 6-(3-Chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

6-(3-Chloro-4-fluorobenzyl)-1-[(dimethylamino)carbonyl]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-3,4-diyl diacetate (30g, 62.7 mmol) was dissolved in 500 mL MeOH and treated with a 30% by weight solution of NaOMe in MeOH (45.2 mL, 251 mmol 4 equivalents was sufficient to get the pH of the reaction to 9) for 1 hour at 40 °C. LCMS showed the cleavage of the acetate groups was complete. The reaction was neutralized with 1N HCl and the volume reduced to remove the MeOH and the residue was diluted with water and acidified to pH 3. The cloudy aqueous layer was diluted with an equal volume (800 mL) of chloroform. After shaking, the product began to crystallize out of the solutions and gathered at the miniscus. The total contents of the funnel were filtered and the collected solids were washed with water until no more salts appeared to remain. The solid was dried *in vacuo* for 16 hrs to give a cinnamon colored solid. The organic layer from the filtered extraction was collected, washed with water and dried over Na_2SO_4, filtered and evaporated. The residue was crystallized from methanol to give product. The crude material was quite insoluble but was crystallized from DMF, then boiled in MeOH, filtered and dried under vacuum to give product.

^1H NMR (400 MHz, DMSO) δ 13.0 (s, 1H), 11.9 (s, 1H), 7.58 (d, J = 6.9 Hz, 1H), 7.38 (m, 2H), 4.69 (bs, 2H), 3.49 (m, 2H), 2.91 (s, 3H), 2.84 (s, 3H), 2.56 (bs, 2H), ppm. (ES MS M+1 = 394.0)

Step 6: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

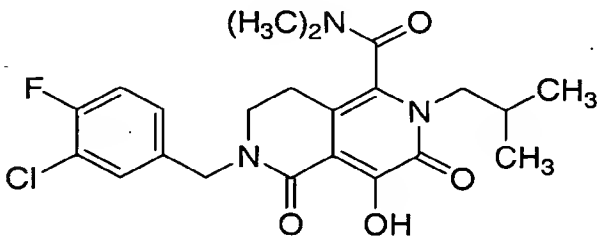
To a solution of 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (3.00 g, 7.62 mmol) in DMSO (86 mL) was added magnesium methylate (42.75 mL of a 6-10% methanol solution, 24.4 mmol), and the reaction was heated

to 60 °C for 0.75 hour. The reaction mixture was reduced on a rotoevaporator to remove all of the MeOH over 45 min. The heat gun was used to drive all MeOH from the bump bulb. The reaction was treated with 2-iodopropane (2.84 mL, 38.1 mmol) and allowed to stir at 60 °C for 3 hours. LCMS showed 11% starting material remaining and over 70% conversion to N- and O-alkylated products (typically 2:1). The reaction was diluted with 350mL EtOAc to which 125 mL 1N HCl was added, and the phases were separated. The aqueous layer was washed once with methylene chloride (100 mL). The combined organic layers were washed with 1N HCl twice more and the organic layer was isolated. The organic layer was washed with 10% aqueous solution of $NaHSO_3$ (3x 100 mL) followed by brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a yellow-orange foam residue. The solid combined with additional crude material from other reactions, dissolved in DMSO and Methanol and purified via reverse phase chromatography using a Biotage 75L canister and a Varian Metaflash 75L C-18 column, eluting with a gradient of 70:30 to 35:65 A:B where A= 0.05% TFA in water and B = 0.05% TFA in acetonitrile (flowrate = 300 mL/min, detection at 214 and 254 nM). Evaporation of the fractions afforded pure oil by HPLC/LCMS and NMR. Crystallization from EtOAc:hexane afforded white, analytically pure product.

^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, *J* = 1.9, 7.2 Hz, 1H), 7.32 (m, 1H), 7.22 (t, *J* = 8.8 Hz, 1H), 4.78 (d, *J* = 14.9 Hz, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.02 (m, 1H), 3.50 (t, *J* = 6.4 Hz, 2H), 3.09 (s, 3H), 3.00 (s, 3H), 2.59 (t, *J* = 6.4 Hz, 2H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.57 (d, *J* = 6.7 Hz, 3H) ppm. (ES MS exact mass M+1 = 436.144)

EXAMPLE 14

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 4-Amino-6-(3-chloro-4-fluorobenzyl)-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

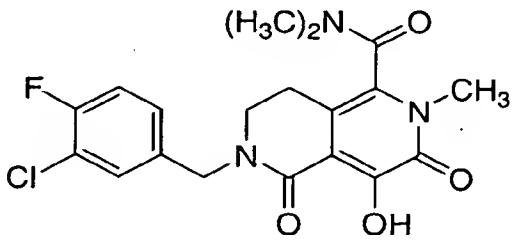
To a solution of 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (0.5 g, 1.27 mmol) in DMSO (10 mL) was added magnesium methylate (5.48 mL of a 6-10% methanol solution, 30.8 mmol), and the reaction was heated

to 60 °C for 0.5 hour. The reaction mixture was rotavapped to remove all of the MeOH. The heat gun was used to drive all MeOH from the bump bulb. The reaction was treated with 1-iodo-2-methylpropane (0.73 mL, 6.35 mmol) and allowed to stir at 60 °C for 40 min. LCMS showed trace starting material remaining and mostly N-alklated product formed (O-alkylated products ~ 3%). The reaction was diluted with 1 mL MeOH then 1 N HCl was added until a precipitate began to form. A 10 mL portion of 10% sodium bisulfite was added and the brown mixture turned green. Water was added and the mixture stirred for 1 hr, then the liquid was decanted off the solids. The solids were partitioned with chloroform 20 mL and 1 N HCl 20 mL. The organic layer was washed 2 times more with 1 N HCl and then with brine, dried over Na_2SO_4, filtered and evaporated to an oil that smelled strongly of alkylating agent. The residue was diluted with toluene and evaporated and pumped on for 4 hrs. The residue would not crystallize from ethyl acetate and methanol. The residue was passed through a Gilson reverse phase column eluting from 95:5 to 5:95 to give an oil after concentration. Crystallization from EtOAc:hexane afforded white, analytically pure product.

^{1}H NMR (400 MHz, DMSO) δ 13.0 (s, 1H), 7.60 (d, J = 4.8 Hz, 1H), 7.40 (t, J = 8.6 Hz, 1H), 7.38 (m, 1H), 4.77 (d, J = 14.7 Hz, 1H), 4.58 (d, J = 14.7 Hz, 1H), 3.90 (dd, J = 7.7, 13.2 Hz, 1H), 3.50 (m, 3H), 2.97 (s, 3H), 2.04 (s, 3H), 2.54 (m, buried), 2.02 (m, 1H), 0.81 (t, J = 6.22 Hz, 6H), ppm. (ES MS exact mass M+1 = 450.151)

EXAMPLE 15

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

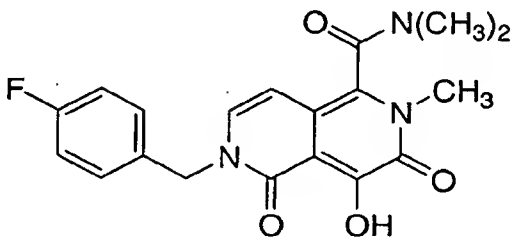
To a solution of 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (0.1 g, 0.254 mmol) in dry DMSO (5 mL) was added magnesium methylate (1.097 mL of a 6-10% methanol solution, 0.792 mmol), and the reaction was heated to 60 °C for 0.5 hour. The reaction mixture was rotavapped to remove all of the MeOH. The heat gun was used to drive all MeOH from the bump bulb. The reaction was treated with methyl iodide (0.079

mL, 6.35 mmol) and allowed to stir at 60 °C overnight. LCMS showed trace starting material remaining and mostly N-alklated product formed (O-alkylated products minor). The reaction was diluted with 0.5 mL MeOH then 1 N HCl was added until a precipitate began to form. A 5 mL portion of 10% sodium bisulfite was added and the brown mixture turned green. Water was added and the mixture stirred for 1 hr, then the mixture was partitioned with chloroform 20 mL and 1 N HCl 20 mL. The organic layer was washed 2 times more with 1 N HCl and then with brine, dried over Na_2SO_4, filtered and evaporated to an oil. The residue was passed through a Gilson reverse phase column eluting from 95:5 to 5:95 to give an oil after concentration.

^{1}H NMR (400 MHz, CD_3OD) δ 7.5 (dd, J = 2.0, 7.1 Hz, 1H), 7.34 (m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 4.78 (d, J = 14.8 Hz, 1H), 4.64 (d, J = 14.8 Hz, 1H), 3.52 (t, J = 6.5 Hz, 2H), 3.45 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.64 (t, J = 6.4 Hz, 2H) ppm.

EXAMPLE 16

6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide

To solution of 5-(ethoxycarbonyl)-2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydro-2,6-naphthyridin-6-ium trifluoroacetate (0.020g, 0.045 mmol; see Example 8, Step 4) in CCl_4 (2 mL) is added N-bromo succinimide (0.017g, 0.095 mmol) and AIBN(catalytic). The reaction is heated to 80 °C for 1 hour, then concentrated and chromatographed on reverse phase to give the product.

Step 2: 6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide

The title compound can be prepared using a sequence of transformations similar to those described for Examples 9 and 10.

EXAMPLE 17

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule. Encapsulated oral compositions containing any one of the compounds of Examples 2-16 can be similarly prepared.

EXAMPLE 18

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds in Examples 1-15 were tested in the integrase assay and were found to have IC_{50}'s less than about 1 micromolar.

Further description on conducting the assay using preassembled complexes is found in Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 19

Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds in Examples 1-15 were found to have IC_{95}'s of less than about 10 micromolar in the present assay.

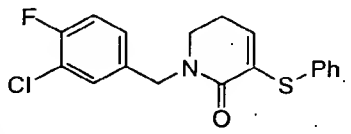
EXAMPLE 20

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

Step 1: 1-(3-Chloro-4-fluorobenzyl)piperidin-2-one

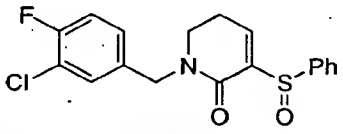
Valerolactam (60 g) was dissolved in MTBE (1.5L) at room temperature. To this solution was added Bu_4NSO_4 (4.9 g) as a phase transfer catalyst. The cloudy solution was stirred at room temperature for 5 minutes. Then, NaOH (50 wt%) was slowly added as to keep the internal temperature below 30°C. Benzylbromide was then added slowly to this biphasic mixture, again as to keep the internal

temperature under control. The reaction was then aged for 4 hours at room temperature. At this time LC showed the reaction to be complete. Water (500 mL) was then added. After phase cut, the organic layer was washed with brine (300 mL), dried under $MgSO_4$ followed by solvent switch to heptane. The slurry obtained was stirred at room temperature. for 1 hour and then filtered to afford the title product.



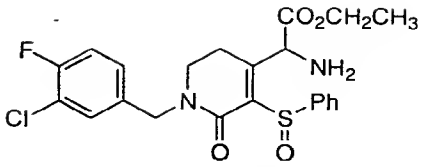
Step 2: Preparation of an unsaturated sulfide of formula **1**:

1-(3-Chloro-4-fluorobenzyl)piperidin-2-one (25g) was dissolved in THF (250 mL) and cooled to -20 degrees C under nitrogen atmosphere. LHMDS (204 mL, 1M in THF) was added over 40 minutes at -20 to -30°C and aged for 1 hour at -20°C. Methyl benzene sulfinate (17.78 g) was added over 30 minutes, again keeping the internal temperature at -20°C. The reaction was aged for 30 minutes at -20°C at which time LC showed the reaction to be complete. The reaction mixture was then quenched with water (100 mL) and diluted with EtOAc (300 mL). After phase cut, the organic layer was washed with HCl 2N (2 x 100 mL). The organic layer was then washed with brine (2 x 100 mL), dried under $MgSO_4$ followed by solvent switch to DCM (final volume 400 mL). To this solution was added acetic anhydride (11.6 mL) and $MeSO_3H$ (3.07 mL). The solution was then aged at room temperature overnight. The reaction was quenched with water (300 mL) and cooled to 0°C. The slurry obtained was then carefully basified to pH=8 with solid Na_2CO_3. The organic layer obtained after phase cut was then washed with brine and dried under $MgSO_4$. After evaporation of solvents, the title unsaturated sulfide **1** was obtained as an oil which solidified on standing. The title sulfide **1** can be crystallized from MeOH.



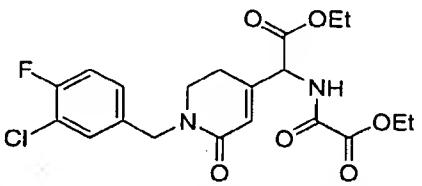
Step 3: Preparation of a vinyl sulfoxide of formula **2**:

Unsaturated sulfide **1** (35.47 g) was dissolved in MeOH (200 mL) and water was added (50 mL) followed by the addition of solid $NaIO_4$ (39.82 g). The slurry obtained was stirred at room temperature for 3 days. The slurry was then filtered and the solid obtained was washed with EtOAc (200 mL). The filtrate was then evaporated until almost dryness and diluted with EtOAc (350 mL) and washed with H_2O (200 mL). The organic layer was then washed with brine (200 mL) and dried under $MgSO_4$. The organic solvents were then removed to completion. The oil obtained was crystallized with a IPAc:Hexane (1: 1.2) mixture and seeding to afford the title sulfoxide **2**.



Step 4: Preparation of a Michael adduct of formula 3:

To a solution of vinyl sulfoxide 2 (5g, 13.74 mmoles) in THF (70 mL) at 0°C was added diphenylketimine glycine ethyl ester (4g, 15.mmoles) followed by t-BuOLi (0.2g, 2.5 mmoles). The mixture was stirred for 20 minutes at 0°C then, HCl 2N (80 mL) was added. The resulting mixture was stirred at 20°C for 20 min and MTBE (160 mL) was added. After phase separation, the aqueous layer was basified to pH=8-9 by addition of solid Na_2CO_3. The resulting aqueous layer was extracted twice with EtOAc (2x100 mL) and the solvent evaporated under reduced pressure to give the title adduct 3 as an oil.



Step 5: Preparation of an oxamate of formula 4:

To a solution of adduct 3 (6.2g, 13.28 mmoles) in THF (70 mL) at 0°C was added triethylamine (2 mL, 14.6 mmoles) followed by dropwise addition of ethyloxalyl chloride (1.55 mL, 13.94 mmoles). The resulting slurry was stirred for 20 minutes at 0°C, then water (50 mL) was added. The mixture was extracted with EtOAc (2x100 mL), then solvent switched to toluene (final volume: 80 mL). The toluene solution was heated to 90°C for 30-45 minutes then passed through a plug of silica gel (50g) using AcOEt/hexanes 1:1 (200 mL), then EtOAc as eluent. After evaporation of the solvents, the title oxamate 4 was obtained.

Step 6: Ethyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a solution of oxamate 4 (2g, 4.5 mmoles) in THF (35 mL) was added LiBr (1.2g, 18.1 mmoles) followed by DABCO (0.76g, 6.8 mmoles). The mixture was stiired for 18 hours at 20°C, then HCl 2N (50 mL) was added and the mixture was extracted with EtOAc (50 mL). Solvents were evaporated under reduced pressure to give the title compound as a pale yellow solid.

Alternative Step 6:

Ethyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a stirred solution of ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (5.0 g; see Example 12, Step 6) and sodium acetate (0.89 g) in acetic acid (90 mL) was added peracetic acid (28 mL). The mixture was then heated at 50°C overnight. The mixture was cooled to 5°C and saturated $NaHSO_4$ (17 mL) added, keeping the temperature at less than 25°C. The mixture was concentrated to 50% original volume and partitioned between tert-butyl methyl ether (100 mL) and water (50 mL). The organic phase collected and the volatiles evaporated. The residue was dissolved in toluene (50 mL) and volatiles evaporated, the residue dissolved in toluene (50 mL) and evaporation repeated. Finally the residue was dissolved in toluene (20 mL). Acetic anhydride (3.9 mL) was added and the mixture heated at reflux until complete by HPLC analysis. The mixture cooled to ambient temperature and sodium ethoxide in ethanol (20 mL) was added. The reaction mixture stirred overnight. 2N HCl (31 mL) was added and the title product isolated by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.6-9.5 (bs, 1H), 7.4 (dd, J = 6.8. 2.4Hz, 1H), 7.2 (m, 1H), 7.15 (t, J = 8.4 Hz, 1H), 4.7 (s, 2H), 4.35 (q, J =7.2Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 3.35 (t, J = 6.4 Hz, 2H), 1.4 (t, J = 7.2 Hz, 3H) ppm.

Step 7: Methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a stirred suspension of ethyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (40g) in DMF (200 mL) was added magnesium methoxide in methanol (100 mL). The mixture heated at 40-50°C for 3 hours. The excess methanol distilled off, and methyl tosylate (18 mL) was added. The reaction mixture was heated at 50°C overnight, then cooled to 25°C, and then quenched into 1N HCl (100 mL). The suspension stirred for 1 hour at ambient temperature. The product was isolated by filtration, and the filter cake washed with water (2 x 100 mL) and then dried on the filter under an atmosphere of nitrogen. The crude product was suspended in methanol (460 mL), heated at reflux temperature for 1 hour, and then allowed to cool to ambient temperature. The product was isolated by filtration and the filter cake washed with cold methanol (2x 40 mL) and dried to give the title product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 1H), 7.35 (dd, J = 2.4, 6.9 Hz, 1H), 7.22-7.18 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 4.67 (s, 2H), 3.92 (s, 3H), 3.54 (s, 3H), 3.43 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H) ppm. (ES MS M+1 = 395.0)

Step 8: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

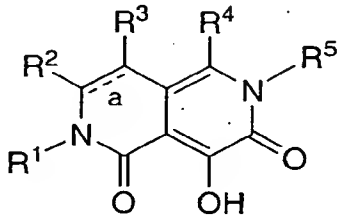
To THF (80mL) cooled to -10°C was added iPrMgCl (2M in THF, 60 mL). Dimethylamine (2M in THF) was then added at -10 to 0°C, the mixture then stirred for 1 hour at -5 to -10°C. The resulting suspension of $ClMgNMe_2$ at -10°C was allowed to warm to 0°C, and a solution of methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (10.0 g) in dichloromethane (100 mL) was added over 20 minutes at 0°C. The mixture was then stirred until reaction was complete by HPLC. The reaction mixture was quenched with 1N HCl (335 mL). The organic layer was collected and the aqueous layer extracted with CH_2Cl_2 (35 mL). The organic phases were then combined and washed with brine (35 mL). Volatiles were evaporated to give the title product as an amorphous solid.

^1H NMR (400 MHz, CD_3OD) δ 7.46 (dd, J = 2.2, 7.14 Hz, 1H), 7.33-7.29 (m, 1H), 7.17 (t, J = 9.0 Hz, 1H), 4.72 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.35 (s, 3H), 3.33-3.96 (m, 2H), 3.07 (s, 3H), 2.97 (s, 3H), 2.47 (dd, J = 5.68,11.36 Hz, 2H) ppm. (ES MS M+1 = 408.0)

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl optionally substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$OC(=O)N(R^a)R^b$, or -$N(R^a)C(=O)N(R^a)R^b$,

(2) -O-C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halogen,

(7) -CN,

(8) -NO_2,

(9) -$N(R^a)R^b$,

(10) -$C(=O)N(R^a)R^b$,

(11) -$C(=O)R^a$,

(12) -CO_2R^a,

(13) -SR^a,
(14) -$S(=O)R^a$,
(15) -SO_2R^a,
(16) -$SO_2N(R^a)R^b$,
(17) -$N(R^a)SO_2R^b$,
(18) -$N(R^a)SO_2N(R^a)R^b$,
(19) -$N(R^a)C(=O)R^b$,
(20) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$, or
(21) -$N(R^a)CO_2R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:
(1) phenyl,
(2) benzyl,
(3) -HetA,
(4) -C(=O)-HetA, or
(5) -HetB;

wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is independently oxo or C_{1-6} alkyl; and

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl substituted with aryl;

R^2 and R^3 are each independently -H or -C_{1-6} alkyl;

R^4 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{1-6} haloalkyl,
(4) -C_{1-6} alkyl substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$C(=O)$-$N(R^a)$-C_{1-6} alkylene-OR^b with the proviso that the -$N(R^a)$- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)$-R^b, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$N(R^a)C(=O)N(R^a)R^b$, or -$OC(=O)N(R^a)R^b$,
(5) -$C(=O)R^a$,
(6) -CO_2R^a,
(7) -$C(=O)N(R^a)R^b$,
(8) -$C(=O)$-$N(R^a)$-C_{1-6} alkylene-OR^b with the proviso that the -$N(R^a)$- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety,
(9) -$N(R^a)$-$C(=O)$-R^b,
(10) -$N(R^a)$-$C(=O)$-$C(=O)N(R^a)R^b$,
(11) -$N(R^a)SO_2R^b$,
(12) -$N(R^a)SO_2N(R^a)R^b$,
(13) -$N(R^a)SO_2N(R^a)R^b$,
(14) -$N(R^a)C(=O)N(R^a)R^b$,
(15) -$OC(=O)N(R^a)R^b$,
(16) -R^K,
(17) -$C(=O)$-R^K,
(18) -$C(=O)N(R^a)$-R^K,
(19) -$C(=O)N(R^a)$-C_{1-6} alkylene-R^K,
(20) -C_{1-6} alkyl substituted with -R^K,
(21) -C_{1-6} alkyl substituted with -$C(=O)$-R^K,
(22) -C_{1-6} alkyl substituted with -$C(=O)N(R^a)$-R^K, or
(23) -C_{1-6} alkyl substituted with -$C(=O)N(R^a)$-C_{1-6} alkylene-R^K;

wherein R^K is

(i) C_{3-8} cycloalkyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(ii) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)R^a$, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(iii) HetK, which is a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 6 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(b) optionally substituted with aryl or HetC;

wherein HetC is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(iv) HetL, which is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^5 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(5) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-N(R^a)R^b, -C_{1-6} alkylene-C(=O)N(R^a)R^b, -C_{1-6} alkylene-C(=O)R^a, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO_2R^a, -$S(O)_nR^a$, or -SO_2N(R^a)R^b,

(6) -C_{1-6} alkyl substituted with HetD, wherein HetD is

(i) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl;

each R^b is independently H or C_{1-6} alkyl; and

each n is independently an integer equal to zero, 1, or 2.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is -CH_2-R^J.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R^J is phenyl optionally substituted with from 1 to 3 substitutents each of which is independently:

(1) -C_{1-4} alkyl,
(2) -C_{1-4} haloalkyl,
(3) -O-C_{1-4} alkyl,
(4) halogen,
(5) -CN,
(6) -C(=O)N(R^a)R^b, or
(7) -SO_2R^a.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^J is 4-fluorophenyl or 3-chloro-4-fluorophenyl.

5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{1-6} fluoroalkyl,
(4) -CO_2R^a,
(5) -C(=O)N(R^a)R^b,
(6) -C(=O)-N(R^a)-$(CH_2)_{2-3}$-OR^b,
(7) -N(R^a)-C(=O)-R^b,
(8) -N(R^a)SO_2R^b,
(9) -N(R^a)SO_2N(R^a)R^b,
(10) -R^K,
(11) -C(=O)-R^K, or
(12) -C(=O)N(R^a)-$(CH_2)_{0-2}$-R^K.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,
(2) -C_{1-4} alkyl,

(3) -C_{3-6} cycloalkyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

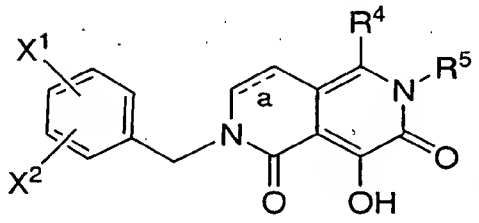
(4) -$(CH_2)_{1-2}$-C_{3-6} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

(5) -$(CH_2)_{1-2}$-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} alkylene-O-C_{1-4} alkyl, -C_{1-4} haloalkyl, or -O-C_{1-4} haloalkyl, or

(6) -$(CH_2)_{1-2}$-HetD, wherein HetD is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or hydroxyl.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both -H.

8. A compound of Formula II, or a pharmaceutically acceptable salt thereof:



(II)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

X^1 and X^2 are each independently:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -O-C_{1-6} alkyl,

(4) -C_{1-6} haloalkyl,

(5) -O-C_{1-6} haloalkyl,

(6) halogen,

(7) -CN,

(8) -$N(R^a)R^b$,

(9) -$C(=O)N(R^a)R^b$,

(10) -$S(O)_nR^a$, wherein n is an integer equal to zero, 1, or 2,

(11) -$N(R^a)SO_2R^b$,

(12) -$N(R^a)SO_2N(R^a)R^b$,

(13) -$N(R^a)C(=O)R^b$,

(14) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$,

(15) -HetA,

(16) -C(=O)-HetA, or

(17) HetB;

wherein each HetA is independently a C_{4-5} azacycloalkyl or a C_{3-4} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-6} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom; and

each HetB is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^4 is:

(1) -CO_2R^a,

(2) -$C(=O)N(R^a)R^b$,

(3) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b,

(4) -$N(R^a)C(=O)R^b$,

(5) -$N(R^a)SO_2R^b$,

(6) -HetK,

(7) -C(=O)-HetK,

(8) -C(=O)N(R^a)-(CH_2)$_{0-1}$-(C_{3-6} cycloalkyl), wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -CF_3, -O-C_{1-6} alkyl, or -OCF_3, or

(9) -C(=O)N(R^a)-CH_2-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -O-C_{1-6} alkyl, -CF_3, -OCF_3, or halogen;

wherein HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

R^5 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{3-6} cycloalkyl,
(4) -CH_2-C_{3-6} cycloalkyl, or
(5) -CH_2-phenyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

9. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein:

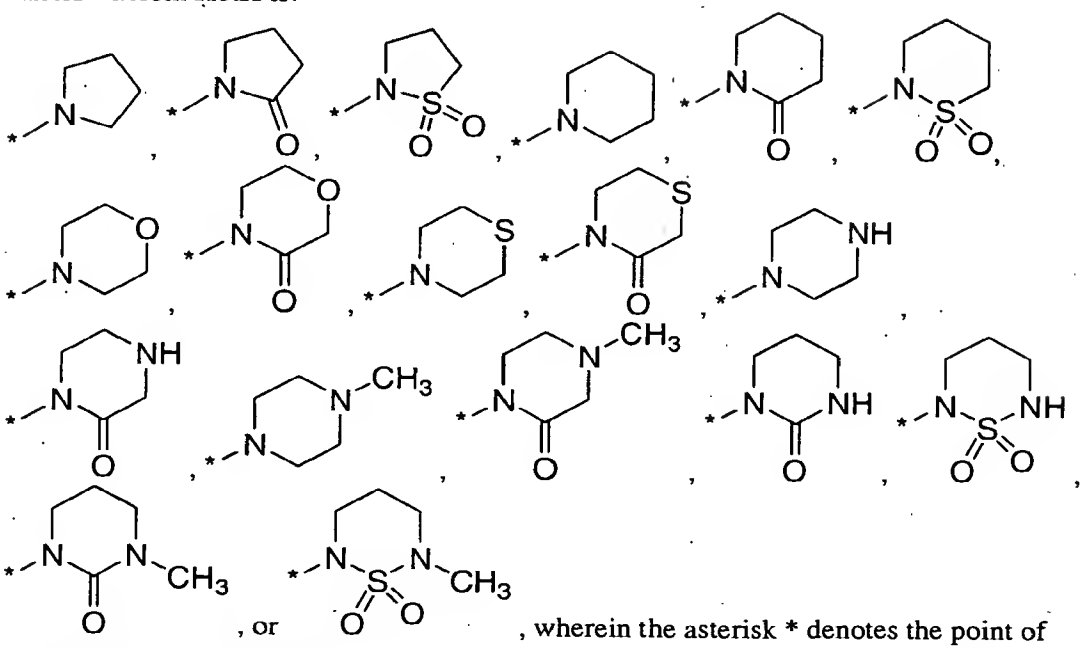
X^1 and X^2 are each independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} alkyl,
(5) halogen,

(6) -CN,
(7) -C(=O)NH_2,
(8) -C(=O)NH(-C_{1-4} alkyl),
(9) -C(=O)N(-C_{1-4} alkyl)$_2$, or
(10) -SO_2-C_{1-4} alkyl;

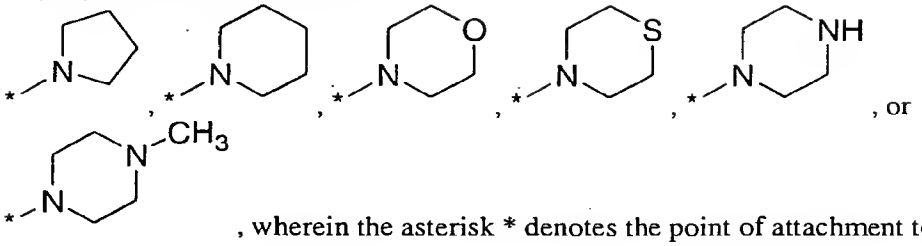
R^4 is:

(1) -CO_2H,
(2) -C(=O)-O-C_{1-4} alkyl,
(3) -C(=O)NH_2,
(4) -C(=O)NH-C_{1-4} alkyl,
(5) -C(=O)N(C_{1-4} alkyl)$_2$,
(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(8) -NHC(=O)-C_{1-4} alkyl,
(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,
(10) -$NHSO_2$-C_{1-4} alkyl,
(11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl,
(12) -HetK wherein HetK is:



, or , wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(15) -C(=O)NH-CH_2-phenyl, or

(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is:

(1) -H,

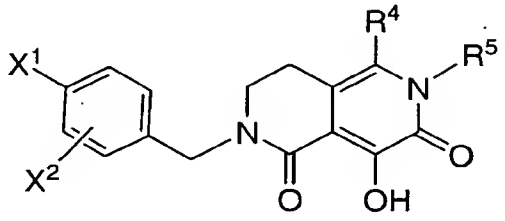
(2) -C_{1-4} alkyl,

(3) -C_{3-6} cycloalkyl,

(4) -CH_2-C_{3-6} cycloalkyl, or

(5) -CH_2-phenyl.

10. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, which is a compound of Formula III:



(III)

wherein:

X^1 is:

(1) -H,

(2) bromo,

(3) chloro,

(4) fluoro, or

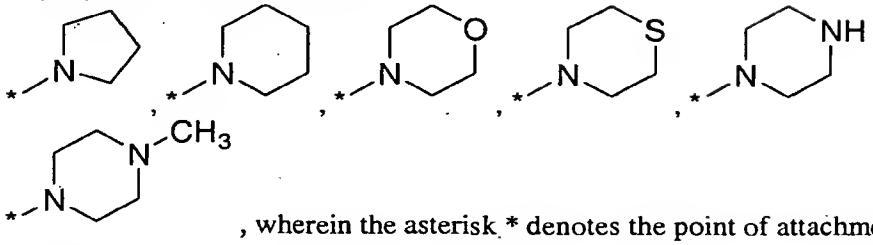
(5) methoxy;

X^2 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro,
(5) methoxy,
(6) -C_{1-4} alkyl,
(7) -CF_3,
(8) -OCF_3,
(9) -CN, or
(10) -$SO_2(C_{1-4}$ alkyl);

R^4 is:

(1) -CO_2H,
(2) -C(=O)-O-C_{1-4} alkyl,
(3) -$C(=O)NH_2$,
(4) -C(=O)NH-C_{1-4} alkyl,
(5) -$C(=O)N(C_{1-4}$ alkyl$)_2$,
(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(8) -NHC(=O)-C_{1-4} alkyl,
(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,
(10) -$NHSO_2$-C_{1-4} alkyl,
(11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl,
(12) -C(=O)-HetK, wherein HetK is:



, or

, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(15) -C(=O)NH-CH_2-phenyl, or

(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is:

(1) -H,

(2) -C_{1-4} alkyl,

(3) cyclopropyl,

(4) cyclobutyl,

(5) -CH_2-cyclopropyl,

(6) -CH_2-cyclobutyl, or

(7) -CH_2-phenyl.

11. The compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein

X^1 is fluoro;

X^2 is -H or chloro;

R^4 is:

(1) -C(=O)-O-C_{1-3} alkyl,

(2) -C(=O)NH-C_{1-3} alkyl,

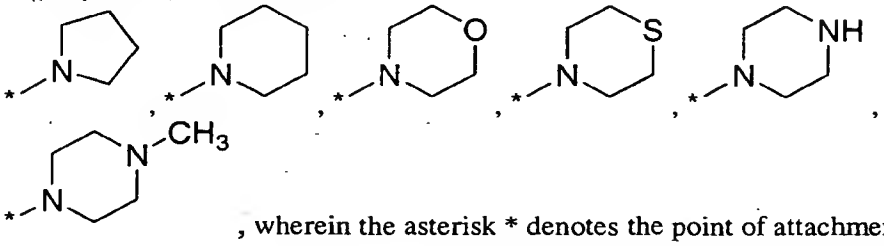
(3) -C(=O)N(C_{1-3} alkyl)$_2$,

(4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl,

(5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl,

(6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl,

(7) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(8) -C(=O)NH-$(CH_2)_{0-1}$-(cyclopropyl),

(9) -C(=O)NH-$(CH_2)_{0-1}$-(cyclobutyl),

(10) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl,

(11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl,

(12) -C(=O)NH-CH_2-phenyl, or

(13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and

R^5 is -H or -C_{1-4} alkyl.

12. The compound according to claim 11, wherein

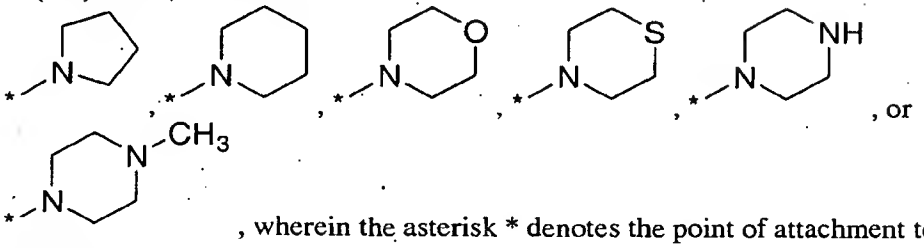
X^1 is fluoro;

X^2 is -H or chloro;

R^4 is:

(1) -C(=O)N(C_{1-3} alkyl)$_2$,

(2) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(3) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl, or

(4) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl; and

R^5 is -C_{1-4} alkyl.

13. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate;

6-(4-fluorobenzyl)-4-hydroxy-*N*,*N*-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-*N*-isopropyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid;

N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide;

N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide;

6-(4-fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide; and

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide.

13. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

15. A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

16. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for inhibiting HIV integrase in a subject in need thereof.

17. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

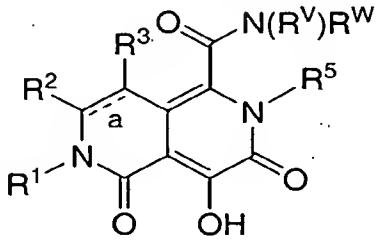
18. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for inhibiting HIV integrase in a subject in need thereof.

19. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

20. A pharmaceutical combination which is (i) a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and (ii) an HIV infection/AIDS antiviral

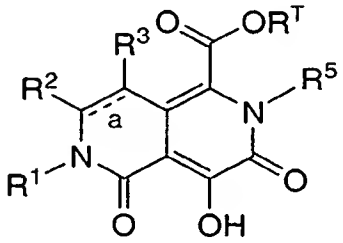
agent selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors; wherein the compound of (i) or its pharmaceutically acceptable salt and the HIV infection/AIDS antiviral agent of (ii) are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for preventing or treating infection by HIV, or for preventing, treating or delaying the onset of AIDS.

21. A process for preparing a compound of Formula IV:



(IV),

which comprises contacting a compound of Formula V:



(V)

with a Grignard salt of an amine of Formula VI:

$$HN(R^V)R^W \quad (VI)$$

to obtain Compound IV; wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl,

(2) -C_{1-6} alkyl substituted with -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -NO_2, -$N(R^a)R^b$, or -$S(O)_nR^a$,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} alkyl,

(5) halogen,

(6) $C(=O)N(R^a)R^b$, or

(7) -SO_2R^a;

(b) optionally substituted with 1 or 2 substituents each of which is independently:

(1) phenyl,

(2) benzyl, or

(3) -HetB;

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl substituted with aryl;

R^2 and R^3 are each independently -H or -C_{1-6} alkyl;

R^5 is:

(1) -C_{1-6} alkyl,

(2) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

(3) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

(4) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} alkyl, or halogen, or

(5) -C_{1-6} alkyl substituted with a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl;

R^T is -C_{1-6} alkyl;

R^V and R^W are each independently -C_{1-6} alkyl or R^V and R^W together with the N atom to which they are both attached form a 4- to 6-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^V and R^W selected from N, O, and S, where the S is optionally oxidized to S(O) or S(O)2, and wherein the saturated heterocyclic ring is optionally substituted with 1 or 2 substituents each of which is independently a C_{1-6} alkyl group;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

22. The process according to claim 21, wherein the Grignard salt is a halomagnesium salt of amine VI.

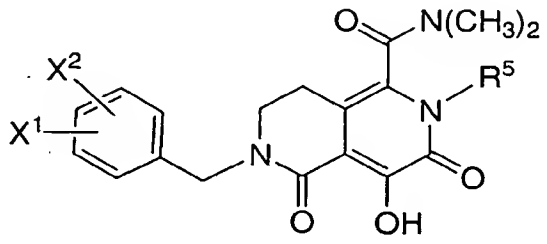
23. The process according to claim 21, wherein the contacting is conducted in an aprotic solvent selected from the group consisting of an alkane, a cycloalkane, a halogenated alkane, a halogenated cycloalkane, an aromatic hydrocarbon, an alkylated aromatic hydrocarbon, a halogenated aromatic hydrocarbon, an alkylated and halogenated aromatic hydrocarbon, an ether, a polyalkyl phosphoramide, an N,N'-dialkylalkyleneurea, and mixtures thereof.

24. The process according to claim 23, wherein the contacting comprises adding Compound V to the Grignard salt of amine VI dissolved or suspended in the aprotic solvent to form a reaction mixture and ageing the reaction mixture.

25. The process according to claim 21, wherein the contacting is conducted at a temperature in a range of from about -20 to about 25°C.

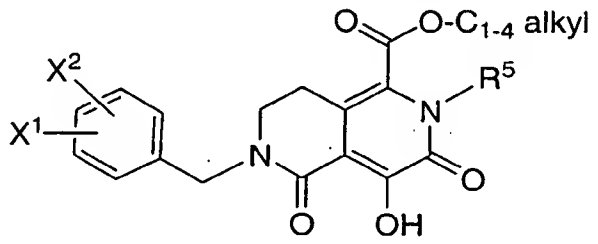
26. The process according to claim 21, wherein the Grignard salt of amine VI is employed in an amount of at least about 2 equivalents per equivalent of Compound V.

27. The process according to claim 21, wherein the compound of Formula IVis a compound of Formula IV-A:



(IV-A);

the compound of Formula V is a compound of Formula V-A:



(V-A);

the Grignard salt is a Grignard salt of dimethylamine;

X^1 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro, or
(5) methoxy;

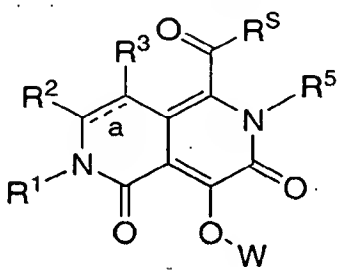
X^2 is:

(1) -H,

(2) bromo,
(3) chloro,
(4) fluoro,
(5) methyl,
(6) methoxy,
(7) $-CF_3$, or
(8) $-OCF_3$; and

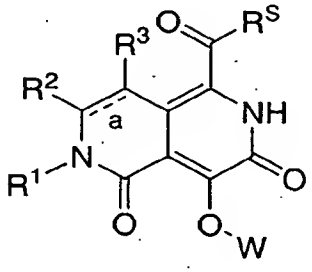
R^5 is $-C_{1-4}$ alkyl.

28. A process for preparing a compound of Formula VII:



(VII)

which comprises reacting an alkylating agent of formula R^5-Z with a compound of Formula VIII:



(VIII)

in a polar aprotic solvent and in the presence of a base selected from a magnesium base and a calcium base; wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

W is -H or $-C_{1-6}$ alkyl;

Z is halogen or -SO_3-Q wherein Q is (i) C_{1-6} alkyl or (ii) phenyl optionally substituted with 1 or 2 substituents each of which is independently a C_{1-6} alkyl;

R^S is -O-C_{1-6} alkyl or $N(R^V)R^W$ wherein R^V and R^W are each independently -C_{1-6} alkyl or R^V and R^W together with the N atom to which they are both attached form a 4- to 6-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^V and R^W selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, and wherein the saturated heterocyclic ring is optionally substituted with 1 or 2 substituents each of which is independently a C_{1-6} alkyl group;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl optionally substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$OC(=O)N(R^a)R^b$, or -$N(R^a)C(=O)N(R^a)R^b$,

(2) -O-C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halogen,

(7) -CN,

(8) -NO_2,

(9) -$N(R^a)R^b$,

(10) -$C(=O)N(R^a)R^b$,

(11) -$C(=O)R^a$,

(12) -CO_2R^a,

(13) -SR^a,

(14) -$S(=O)R^a$,

(15) -SO_2R^a,

(16) $-SO_2N(R^a)R^b$,

(17) $-N(R^a)SO_2R^b$,

(18) $-N(R^a)SO_2N(R^a)R^b$,

(19) $-N(R^a)C(=O)R^b$,

(20) $-N(R^a)C(=O)-C(=O)N(R^a)R^b$, or

(21) $-N(R^a)CO_2R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:

(1) phenyl,

(2) benzyl,

(3) -HetA,

(4) -C(=O)-HetA, or

(5) -HetB;

wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is independently oxo or C_{1-6} alkyl; and

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or hydroxy; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or hydroxy; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or $-C_{1-6}$ alkyl substituted with aryl;

R^2 and R^3 are each independently -H or $-C_{1-6}$ alkyl;

R^5 is:

(1) $-C_{1-6}$ alkyl,

(2) $-C_{3-8}$ cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently $-C_{1-6}$ alkyl or $-O-C_{1-6}$ alkyl,

(3) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or -O-C_{1-6} alkyl,

(4) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} alkyl, or halogen, or

(5) -C_{1-6} alkyl substituted with a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl;

each R^b is independently H or C_{1-6} alkyl; and

each n is independently an integer equal to zero, 1, or 2.

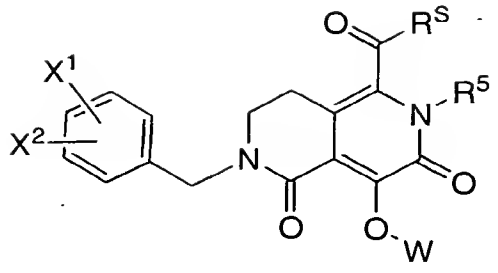
29. The process according to claim 28, wherein the base comprises a magnesium base which is $Mg(R^X)_2$, wherein each R^X is independently H or -O-C_{1-6} alkyl.

30. The process according to claim 28, wherein the polar aprotic solvent comprises a halogenated alkane, an ether, an ester, a tertiary amide, an N-alkylpyrrolidone, a sulfoxide, or a nitrile.

31. The process according to claim 28, wherein the reaction is conducted at a temperature in a range of from about -20 to about 100 °C.

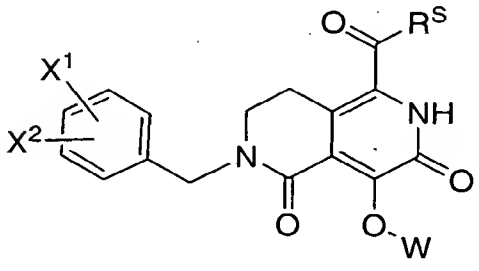
32. The process according to claim 28, wherein the alkylating agent of formula R^1-Z is employed in an amount in a range of from about 0.5 to about 20 equivalents per equivalent of Compound VIII.

33. The process according to claim 28, wherein the compound of Formula VII is a compound of Formula VII-A:



(VII-A)

the compound of Formula VIII is a compound of Formula VIII-A:



(VIII-A);

wherein:

W is -H or -C_{1-6} alkyl;

X^1 and X^2 are each independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} alkyl,
(5) halogen,
(6) -CN,
(7) -C(=O)NH_2,
(8) -C(=O)NH(-C_{1-4} alkyl),
(9) -C(=O)N(-C_{1-4} alkyl)$_2$, or
(10) -SO_2-C_{1-4} alkyl;

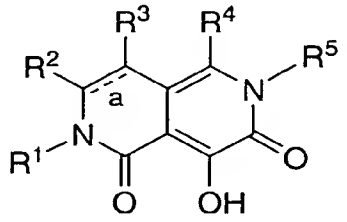
Z is -Cl, -Br, -I, or tosylate;

R^S is -O-C_{1-6} alkyl or $N(R^V)R^W$ wherein R^V and R^W are each independently -C_{1-6} alkyl; and

R^5 is -C_{1-6} alkyl.

ABSTRACT OF THE DISCLOSURE

Hydroxy (tetra- or hexa-)hydronaphthyridine dione compounds of Formula I are inhibitors of HIV integrase and inhibitors of HIV replication:



(I)

wherein a, R^1, R^2, R^3, R^4 and R^5 are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.